

## **97 Human Secreted Proteins**

### **Cross-Reference To Related Applications**

**[0001]** This application is a continuation of U.S. Patent Application No. 09/948,783, filed September 10, 2001, which claims benefit under 35 U.S.C. § 119(e) of U.S. Provisional Patent Application No. 60/231,846 filed September 11, 2000; this application is also a continuation-in-part of U.S. Patent Application No. 09/892,877 filed June 28, 2001, which is a continuation application of U.S. Patent Application No. 09/437,658 filed November 10, 1999, which is a continuation-in-part of International Patent Application No: PCT/US99/09847, filed May 6, 1999, which claims benefit under 35 U.S.C. § 119(e) based on the following U.S. Provisional Applications: No. 60/085,093, filed on May 12, 1998; No. 60/085,094, filed on May 12, 1998; No. 60/085,105, filed on May 12, 1998; No. 60/085,180, filed on May 12, 1998; No. 60/085,927, filed on May 18, 1998; No. 60/085,906, filed on May 18, 1998; No. 60/985,920, filed on May 18, 1998; No. 60/085,924, filed on May 18, 1998; No. 60/085,922, filed on May 18, 1998; No. 60/085,923, filed on May 18, 1998; No. 60/085,921, filed on May 18, 1998; No. 60/085,925, filed on May 18, 1998; and, No. 60/085,928, filed on May 18, 1998. Each of the above referenced patents and/or patent applications is hereby incorporated by reference in its entirety.

### ***Field of the Invention***

**[0002]** This invention relates to newly identified polynucleotides, polypeptides encoded by these polynucleotides, antibodies that bind these polypeptides, uses of such polynucleotides, polypeptides, and antibodies, and their production.

### ***Background of the Invention***

**[0003]** Unlike bacterium, which exist as a single compartment surrounded by a membrane, human cells and other eucaryotes are subdivided by membranes into many functionally distinct compartments. Each membrane-bounded compartment, or organelle, contains different proteins essential for the function of the organelle. The

cell uses "sorting signals," which are amino acid motifs located within the protein, to target proteins to particular cellular organelles.

[0004] One type of sorting signal, called a signal sequence, a signal peptide, or a leader sequence, directs a class of proteins to an organelle called the endoplasmic reticulum (ER). The ER separates the membrane-bounded proteins from all other types of proteins. Once localized to the ER, both groups of proteins can be further directed to another organelle called the Golgi apparatus. Here, the Golgi distributes the proteins to vesicles, including secretory vesicles, the cell membrane, lysosomes, and the other organelles.

[0005] Proteins targeted to the ER by a signal sequence can be released into the extracellular space as a secreted protein. For example, vesicles containing secreted proteins can fuse with the cell membrane and release their contents into the extracellular space - a process called exocytosis. Exocytosis can occur constitutively or after receipt of a triggering signal. In the latter case, the proteins are stored in secretory vesicles (or secretory granules) until exocytosis is triggered. Similarly, proteins residing on the cell membrane can also be secreted into the extracellular space by proteolytic cleavage of a "linker" holding the protein to the membrane.

[0006] Despite the great progress made in recent years, only a small number of genes encoding human secreted proteins have been identified. These secreted proteins include the commercially valuable human insulin, interferon, Factor VIII, human growth hormone, tissue plasminogen activator, and erythropoietin. Thus, in light of the pervasive role of secreted proteins in human physiology, a need exists for identifying and characterizing novel human secreted proteins and the genes that encode them. This knowledge will allow one to detect, to treat, and to prevent medical diseases, disorders, and/or conditions by using secreted proteins or the genes that encode them.

### ***Summary of the Invention***

[0007] The present invention relates to novel polynucleotides and the encoded polypeptides. Moreover, the present invention relates to vectors, host cells, antibodies, and recombinant and synthetic methods for producing the polypeptides



and polynucleotides. Also provided are diagnostic methods for detecting diseases, disorders, and/or conditions related to the polypeptides and polynucleotides, and therapeutic methods for treating such diseases, disorders, and/or conditions. The invention further relates to screening methods for identifying binding partners of the polypeptides.

### ***Detailed Description***

#### **[0008] Definitions**

[0009] The following definitions are provided to facilitate understanding of certain terms used throughout this specification.

[0010] In the present invention, "isolated" refers to material removed from its original environment (e.g., the natural environment if it is naturally occurring), and thus is altered "by the hand of man" from its natural state. For example, an isolated polynucleotide could be part of a vector or a composition of matter, or could be contained within a cell, and still be "isolated" because that vector, composition of matter, or particular cell is not the original environment of the polynucleotide. The term "isolated" does not refer to genomic or cDNA libraries, whole cell total or mRNA preparations, genomic DNA preparations (including those separated by electrophoresis and transferred onto blots), sheared whole cell genomic DNA preparations or other compositions where the art demonstrates no distinguishing features of the polynucleotide/sequences of the present invention.

[0011] In the present invention, a "secreted" protein refers to those proteins capable of being directed to the ER, secretory vesicles, or the extracellular space as a result of a signal sequence, as well as those proteins released into the extracellular space without necessarily containing a signal sequence. If the secreted protein is released into the extracellular space, the secreted protein can undergo extracellular processing to produce a "mature" protein. Release into the extracellular space can occur by many mechanisms, including exocytosis and proteolytic cleavage.

[0012] In specific embodiments, the polynucleotides of the invention are at least 15, at least 30, at least 50, at least 100, at least 125, at least 500, or at least 1000 continuous nucleotides but are less than or equal to 300 kb, 200 kb, 100 kb, 50 kb, 15

kb, 10 kb, 7.5 kb, 5 kb, 2.5 kb, 2.0 kb, or 1 kb, in length. In a further embodiment, polynucleotides of the invention comprise a portion of the coding sequences, as disclosed herein, but do not comprise all or a portion of any intron. In another embodiment, the polynucleotides comprising coding sequences do not contain coding sequences of a genomic flanking gene (i.e., 5' or 3' to the gene of interest in the genome). In other embodiments, the polynucleotides of the invention do not contain the coding sequence of more than 1000, 500, 250, 100, 50, 25, 20, 15, 10, 5, 4, 3, 2, or 1 genomic flanking gene(s).

[0013] As used herein, a "polynucleotide" refers to a molecule having a nucleic acid sequence contained in SEQ ID NO:X or the cDNA contained within the clone deposited with the ATCC. For example, the polynucleotide can contain the nucleotide sequence of the full length cDNA sequence, including the 5' and 3' untranslated sequences, the coding region, with or without the signal sequence, the secreted protein coding region, as well as fragments, epitopes, domains, and variants of the nucleic acid sequence. Moreover, as used herein, a "polypeptide" refers to a molecule having the translated amino acid sequence generated from the polynucleotide as broadly defined.

[0014] In the present invention, the full length sequence identified as SEQ ID NO:X was often generated by overlapping sequences contained in multiple clones (contig analysis). A representative clone containing all or most of the sequence for SEQ ID NO:X was deposited with the American Type Culture Collection ("ATCC"). As shown in Table 1, each clone is identified by a cDNA Clone ID (Identifier) and the ATCC Deposit Number. The ATCC is located at 10801 University Boulevard, Manassas, Virginia 20110-2209, USA. The ATCC deposit was made pursuant to the terms of the Budapest Treaty on the international recognition of the deposit of microorganisms for purposes of patent procedure.

[0015] A "polynucleotide" of the present invention also includes those polynucleotides capable of hybridizing, under stringent hybridization conditions, to sequences contained in SEQ ID NO:X, the complement thereof, or the cDNA within the clone deposited with the ATCC. "Stringent hybridization conditions" refers to an overnight incubation at 42 degree C in a solution comprising 50% formamide, 5x SSC

(750 mM NaCl, 75 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10% dextran sulfate, and 20  $\mu$ g/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1x SSC at about 65 degree C.

[0016] Also contemplated are nucleic acid molecules that hybridize to the polynucleotides of the present invention at lower stringency hybridization conditions. Changes in the stringency of hybridization and signal detection are primarily accomplished through the manipulation of formamide concentration (lower percentages of formamide result in lowered stringency); salt conditions, or temperature. For example, lower stringency conditions include an overnight incubation at 37 degree C in a solution comprising 6X SSPE (20X SSPE = 3M NaCl; 0.2M  $\text{NaH}_2\text{PO}_4$ ; 0.02M EDTA, pH 7.4), 0.5% SDS, 30% formamide, 100  $\mu$ g/ml salmon sperm blocking DNA; followed by washes at 50 degree C with 1XSSPE, 0.1% SDS. In addition, to achieve even lower stringency, washes performed following stringent hybridization can be done at higher salt concentrations (e.g. 5X SSC).

[0017] Note that variations in the above conditions may be accomplished through the inclusion and/or substitution of alternate blocking reagents used to suppress background in hybridization experiments. Typical blocking reagents include Denhardt's reagent, BLOTTO, heparin, denatured salmon sperm DNA, and commercially available proprietary formulations. The inclusion of specific blocking reagents may require modification of the hybridization conditions described above, due to problems with compatibility.

[0018] Of course, a polynucleotide which hybridizes only to polyA+ sequences (such as any 3' terminal polyA+ tract of a cDNA shown in the sequence listing), or to a complementary stretch of T (or U) residues, would not be included in the definition of "polynucleotide," since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone generated using oligo dT as a primer).

[0019] The polynucleotide of the present invention can be composed of any polyribonucleotide or polydeoxiribonucleotide, which may be unmodified RNA or DNA or modified RNA or DNA. For example, polynucleotides can be composed of

single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, the polynucleotide can be composed of triple-stranded regions comprising RNA or DNA or both RNA and DNA. A polynucleotide may also contain one or more modified bases or DNA or RNA backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications can be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically, or metabolically modified forms.

**[0020]** The polypeptide of the present invention can be composed of amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres, and may contain amino acids other than the 20 gene-encoded amino acids. The polypeptides may be modified by either natural processes, such as posttranslational processing, or by chemical modification techniques which are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications can occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present in the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched, for example, as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched, and branched cyclic polypeptides may result from posttranslation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cysteine, formation of pyroglutamate, formylation,

gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, pegylation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination. (See, for instance, PROTEINS - STRUCTURE AND MOLECULAR PROPERTIES, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York (1993); POSTTRANSLATIONAL COVALENT MODIFICATION OF PROTEINS, B. C. Johnson, Ed., Academic Press, New York, pgs. 1-12 (1983); Seifter et al., Meth Enzymol 182:626-646 (1990); Rattan et al., Ann NY Acad Sci 663:48-62 (1992).)

[0021] "SEQ ID NO:X" refers to a polynucleotide sequence while "SEQ ID NO:Y" refers to a polypeptide sequence, both sequences identified by an integer specified in Table 1.

[0022] "A polypeptide having biological activity" refers to polypeptides exhibiting activity similar, but not necessarily identical to, an activity of a polypeptide of the present invention, including mature forms, as measured in a particular biological assay, with or without dose dependency. In the case where dose dependency does exist, it need not be identical to that of the polypeptide, but rather substantially similar to the dose-dependence in a given activity as compared to the polypeptide of the present invention (i.e., the candidate polypeptide will exhibit greater activity or not more than about 25-fold less and, preferably, not more than about tenfold less activity, and most preferably, not more than about three-fold less activity relative to the polypeptide of the present invention.)

**[0023] Polynucleotides and Polypeptides of the Invention**

**[0024] FEATURES OF PROTEIN ENCODED BY GENE NO: 1**

[0025] In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

WAGTQEPTGLPSTLSRSESWDH (SEQ ID NO: 225). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical

to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

[0026] The translation product of this gene shares sequence homology with tag-7 which is thought to be important in tumor metastasis and is itself a secretory protein (see, Kiselev SL, et al., J Biol Chem. 273:18633 (1998) and Genetika. 1996 May; 32(5): 621-628. (Russian)), and a family of peptidoglycan recognition proteins involved in the innate immune response to peptidoglycan in species as diverse as insects and humans (see, Kang, D. et.al., PNAS 95:10078 (1998)).

[0027] This gene is expressed primarily in keratinocytes.

[0028] Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, dermatological disorders, especially skin cancers such as melanoma. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the integumentary system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., skin, cancerous and wounded tissues) or bodily fluids (e.g., sweat, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one, two, or all three of the immunogenic epitopes shown in SEQ ID NO: 118 as residues: Ser-25 to Ala-31, Gln-146 to Ser-151, His-231 to Asn-236. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

[0029] The tissue distribution in keratinocytes and homology to tag-7 indicates that polynucleotides and polypeptides corresponding to this gene would be useful for

detection, treatment, and/or prevention of dermatological disorders, especially skin cancers like melanoma, and integumentary tumors (e.g., keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis fungoides, and Kaposi's sarcoma). Tag-7 was discovered when gene expression was compared in a metastatic (VMR-Liv) neoplastic cell line and a related nonmetastatic (VMR-O) neoplastic cell line by means of the differential display method. A fragment of cDNA corresponding to the tag-7 gene, differentially expressed in the metastatic cell line, was isolated. The full-length tag-7 cDNA was cloned and its nucleotide sequence was determined. The gene sequence claimed in this patent application has significant homology to tag-7 and on that basis is expected to share significant biological activities with tag-7. Such activities can be assayed as set forth herein and by assays known in the art. Additionally, the homology to a conserved peptidoglycan recognition protein family involved in innate immunity, indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the treatment, diagnosis, and/or prevention of various skin disorders including congenital disorders (e.g., nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), injuries and inflammation of the skin (e.g., wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (e.g., lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. Moreover, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (e.g., cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athlete's foot, and ringworm). Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0030]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:11 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1177 of SEQ ID NO:11, b is an integer of 15 to 1191, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:11, and where b is greater than or equal to a + 14.

**[0031] FEATURES OF PROTEIN ENCODED BY GENE NO: 2**

**[0032]** The translation product of this gene shares weak sequence homology with FGF Receptor Ligand-2 which is thought to be important in activating FGF receptor in mediating cell proliferative functions.

**[0033]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group:

EIIHNLPTSRMAARTKKKNDIINIKVPADCNTRMSYYYKGSGKRGEMESWLVMSSWSILDFEFLEARPQLFNLVYTEHSTYSGRHYTRERGGFMVFKNSYSQLLLKRKDSLCAFIQPMALNIIHVPMSKCIFPAQSGPSTFRSLWWCPHPISKCQLGLYSSQIRDIPYLA (SEQ ID NO: 226),

EIIHNLPTSRMAARTKKKNDIINIKVPADCNTRMS (SEQ ID NO: 227),

YYYKGSGKRGEMESWLVMSSWSILDFEFLEARPQLF (SEQ ID NO: 228),

NLVYTEHSTYSGRHYTRERGGFMVFKNSYSQLLLKR (SEQ ID NO: 229),

KDSLCAFIQPMALNIIHVPMSKCIFPAQSGPSTF (SEQ ID NO: 230), and/or

RSLWWCPHPISKCQLGLYSSQIRDIPYLA (SEQ ID NO: 231). Moreover,

fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of



the invention and polynucleotides encoding these polypeptides are also encompassed by the invention. This gene is expressed primarily in neutrophils.

**[0034]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, abnormal immune reactions or disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system tissue and connective tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of the immunogenic epitopes shown in SEQ ID NO: 119 as residues: Met-1 to Met-6. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0035]** The tissue distribution and homology to FGF Receptor Ligand-2 indicates that polynucleotides and polypeptides corresponding to this gene would be useful for detection, treatment, and/or prevention of immune disorders, especially those that are mediated by neutrophil functions. They can be utilized in the treatment of neural and immune disorders, or to stimulate proliferation of vertebrate cells, raise antibodies, and to screen for antagonists useful for inhibiting tumor growth. Moreover, the expression of this gene product indicates a role in regulating the proliferation, survival, differentiation, and/or activation of hematopoietic cell lineages, including blood stem cells. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Representative uses are described in the "Immune Activity" and "Infectious Disease"

sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0036]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:12 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1237 of SEQ ID NO:12, b is an integer of 15 to 1251, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:12, and where b is greater than or equal to a + 14.

### **[0037] FEATURES OF PROTEIN ENCODED BY GENE NO: 3**

[0038] The translation product of this gene shares sequence homology with glycosyl transferase, which is thought to be important in glycosylation of proteins (see, e.g., Genbank Accession No. g2996578). Based on the sequence similarity, the translation product of this clone is expected to share at least some biological activities with glycosyltransferase proteins. Such activities are known in the art.

[0039] The polypeptide of this gene has been determined to have transmembrane domains at about amino acid positions 238-254, 338-354, 143-159, 13-29, 429-445, 384-400, 489-505, 462-478, 102-118, and 189-205 of the amino acid sequence referenced in Table 1 for this gene. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type IIIa membrane proteins.

[0040] The gene encoding the disclosed cDNA is believed to reside on chromosome 11. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 11.

[0041] In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group:

EACGAAAMAALTIATGTGNWFSALALGVTLKCLLIPTYHSTDFEVHRNWL  
AITHSLPISQWYYEATSEWTLDYPPFFAWFEYILSHVAKYFDQEMLNVHNLN  
YSSSRTLTFQRFSVIFMDVLFVYAVRECKCIDGKKVGKELTEKPKFILSVLLL  
WNFGLLIVDHIHFQYNGFLFGLMLLSIARLFQKRHMEGAFLFAVLLHFKHIYL  
YVAPAYGVYLLRSYCFTANKPDGSIRWKSFSFVRVISLGLVVFLVSALS LGPF  
LALNQLPQVFSRLFPFKRGLCHAYWAPNFWALYNALDKVLSVIGLKLKFLDP  
NNIPKASMTSGLVQQFQHTVLPSTPLATLICTLIAILPSIFCLWFKPQGPRGFL  
RCLTLCALSSFMFGWHVHEKAILLAILPMSLLSVGKAGDASIFLILTTTGHYSL  
FPLLFTAPELPIKILLMLLFTIYSSSLKTLFRKEKPLFNWMETFYLLXLGPLEVC  
CEFVFPFTSW KVKYPFIPLLLTSVYCAVGITYAWFKLYVSVLIDSAIGKTKKQ  
(SEQ ID NO: 232). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention.

Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0042]** This gene is expressed primarily in osteoclastoma cells, B-cells, macrophage, tonsils, ovarian cancer tissue, melanocytes, haemopoietic cells and colon tissue, and, to a lesser extent, in several other tissues and organs.

**[0043]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the skin, blood, skeletal system and cancer. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the haemopoietic system, epithelium and skeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, musculo-skeletal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one, two, three, four or all five of the immunogenic epitopes shown in SEQ ID NO: 120 as residues: Glu-136 to Pro-141, Ala-221 to Ser-227, Asp-307 to Pro-312, Lys-355 to Gly-361, Phe-449 to Pro-454. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0044]** The tissue distribution in musculo-skeletal and immune tissues, and the homology to glycosyl transferase protein, indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the treatment, prevention, detection and/or diagnosis of disorders of the haemopoietic, skeletal and epithelial systems, and cancers thereof, as well as disorders associated with incorrect post-translational modification of proteins (i.e. glycosylation). The tissue distribution in immune cells (e.g., B-cells and macrophage) indicates polynucleotides and

polypeptides corresponding to this gene would be useful for the diagnosis detection, prevention and/or treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. Involvement in the regulation of cytokine production, antigen presentation, or other processes indicates a usefulness for treatment of cancer (e.g. by boosting immune responses). Expression in cells of lymphoid origin, indicates the natural gene product would be involved in immune functions. Therefore it would also be useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0045]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:13 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the

general formula of a-b, where a is any integer between 1 to 1720 of SEQ ID NO:13, b is an integer of 15 to 1734, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:13, and where b is greater than or equal to a + 14.

**[0046] FEATURES OF PROTEIN ENCODED BY GENE NO: 4**

[0047] The translation product of this gene shares sequence homology with human pleckstrin protein which is thought to be important in platelet formation or activity (see, e.g., Genbank Accession No. g35518 and Tyers, M., et al., Nature 333 (6172), 470-473 (1988); all references available through this accession are hereby incorporated herein by reference). Therefore, it is likely that this gene also has activity in platelets.

[0048] This gene is expressed primarily in keratinocytes, and, to a lesser extent, in spleen and bone marrow.

[0049] Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of the following diseases and conditions which include, but are not limited to, immune and clotting disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and blood clotting systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, blood clotting, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one or both of the immunogenic epitopes shown in SEQ ID NO: 121 as residues: Leu-38 to Gly-49, Lys-75 to Thr-80. Polynucleotides encoding said

polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0050]** The tissue distribution in keratinocytes, spleen and bone marrow, and the homology to pleckstrin indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the study, diagnosis, detection, prevention and/or treatment of immune system and clotting disorders. Furthermore, since this protein is 50% identical to the Pleckstrin protein, it is an excellent candidate for a protein kinase C substrate. Identification of this protein as a target of protein kinase C, and the exploration of its role in protein kinase C mediated responses, such as inflammation, may lead to a better understanding of the inflammatory response. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0051]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:14 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1526 of SEQ ID NO:14, b is an integer of 15 to 1540, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:14, and where b is greater than or equal to a + 14.

#### **[0052] FEATURES OF PROTEIN ENCODED BY GENE NO: 5**

**[0053]** The gene encoding the disclosed cDNA is thought to reside on chromosome 17. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 17.

**[0054]** This gene is expressed primarily in infant liver/spleen tissues, T cells, bone marrow stromal cells, and thymus tissue, and, to a lesser extent, in brain and tonsils tissues.

**[0055]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, various immune system disorders and/or diseases. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of the immunogenic epitopes shown in SEQ ID NO: 122 as residues: Ser-46 to Arg-54. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0056]** The tissue distribution in liver/spleen tissues, T-cells, bone marrow stromal cells, and thymus tissue indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis, detection, prevention and/or treatment of a variety of cancers, most notably cancers of the immune system. Representative uses are described in the Immune Activity and Infectious Disease sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product in a variety of cells of the immune system indicates that polynucleotides and polypeptides corresponding to this gene may be players in the progression of these diseases, and may be a beneficial target for inhibitors as therapeutics. Furthermore, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the



treatment and/or diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia, since stromal cells are important in the production of cells of hematopoietic lineages. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[0057] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:15 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1544 of SEQ ID NO:15, b is an integer of 15 to 1558, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:15, and where b is greater than or equal to a + 14.

#### **[0058] FEATURES OF PROTEIN ENCODED BY GENE NO: 6**

[0059] The translation product of this gene shares sequence homology with angiopoietin-2, an anti-angiogenic factor. See, for example, Maisonpierre, et al., Angiopoietin-2, a natural antagonist for Tie2 that disrupts in vivo angiogenesis. Science. (1997) 277(5322): 55-60, incorporated herein by reference in its entirety.

Based on the sequence similarity, the translation product of this gene is expected to share certain biological activities with Angiopoietin-2 as may be assessed by assays known in the art and described herein.

[0060] In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group:

MFTIKLLLFIVPLVISSRIDQDNSSFDSLSPEPKSRFAMLDDVKILANGLLQLGH  
GLKDFVHKTGQINDIFQKLNIFDQSFYDLSLQTSEIKEEEKELRRTTYKLQVK  
NEEVKNMSLELNSKLESLLKILLQKQVKYLEEQLTNLIQNQPETPEHPEVTS  
LKTFVEKQDNSIKDLLQTVEDQYKQLNQHSQIKEIENQLRRTSIQEPTEISLSS  
KPRAPRTTPFLQLNEIRNVKHDGIPAECTTIYNRGEHTSGMYAIRPSNSQVFHV  
YCDVISGSPWTLIQHRIDGSQNFNETWENYKYGFGRLDGEFWLGLEKIYSIVK  
QSNYVLRIELEDWKDNKHIEYSFYLGNETNYTLHLVAITGNVPNAIPENK  
DLVFSTWDHKAKGHFNCPEGYSGGWWHDECGENNLNGKYNKPRAKSKP  
ERRRGLSWKSQNGRLYSIKSTKMLIHPTDSESFE (SEQ ID NO: 233),  
MFTIKLLLFIVPLVISSRIDQDNSSFDSLSPEPKSRF (SEQ ID NO: 234),  
AMLDDVKILANGLLQLGHGLKDFVHKTGQINDI (SEQ ID NO: 235),  
FQKLNIFDQSFYDLSLQTSEIKEEEKELRRTTYKL (SEQ ID NO: 236),  
QVKNEEVKNMSLELNSKLESLLKILLQKQVKYLE (SEQ ID NO: 237),  
EQLTNLIQNQPETPEHPEVTSLKTFVEKQDNSIKDL (SEQ ID NO: 238),  
LQTVEDQYKQLNQHSQIKEIENQLRRTSIQEPTE (SEQ ID NO: 239),  
ISLSSKPRAPRTTPFLQLNEIRNVKHDGIPAECTT (SEQ ID NO: 240),  
IYNRGEHTSGMYAIRPSNSQVFHVYCDVISGSPWTL (SEQ ID NO: 241),  
IQHRIDGSQNFNETWENYKYGFGRLDGEFWLGLEKI (SEQ ID NO: 242),  
YSIVKQSNYVLRIELEDWKDNKHIEYSFYLGNETNYTLHLVAITGNVPNAIPENK (SEQ ID NO: 243),  
TNYTLHLVAITGNVPNAIPENKDLVFSTWDHKAKG (SEQ ID NO: 244),  
HFNCPEGYSGGWWHDECGENNLNGKYNKPRAKSKP (SEQ ID NO: 245),  
and/or ERRRGLSWKSQNGRLYSIKSTKMLIHPTDSESFE (SEQ ID NO: 246).

Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide

encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

[0061] The gene encoding the disclosed cDNA is believed to reside on chromosome 1. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 1.

[0062] This gene is expressed primarily in liver.

[0063] Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, angiogenesis and neovascularisation associated with tumour development.

Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., vascular, liver, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one, two, three or all four of the immunogenic epitopes shown in SEQ ID NO: 123 as residues: Arg-18 to Asp-27, Leu-29 to Arg-36, Ser-90 to Tyr-104, Val-108 to Lys-114.

Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

[0064] The tissue distribution primarily in liver and homology to angiopoietin-2 indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the treatment, prevention, diagnosis and/or detection of disorders associated with angiogenesis including the inhibition of angiogenesis and neovascularisation associated with tumour development; the promotion of neovascularisation and wound healing; the treatment of ischaemia; thromboembolytic disease; atherosclerosis;

inflammation; and diabetes. Moreover, polynucleotides and polypeptides corresponding to this gene may be useful for treating disorders and/or disease states that include, but are not limited to, solid tumors, blood born tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, and uveitis, delayed wound healing, endometriosis, vasculogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophilic joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (Rochelle minalia quintosa), ulcers (*Helicobacter pylori*), Bartonellosis and bacillary angiomatosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0065]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:16 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1622 of SEQ ID NO:16, b

is an integer of 15 to 1636, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:16, and where b is greater than or equal to a + 14.

**[0066] FEATURES OF PROTEIN ENCODED BY GENE NO: 7**

**[0067]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

LPPRGPATFGSPGCPPANSPPSAPATPE PARAPERV (SEQ ID NO: 247).

Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0068]** When tested against fibroblast cell lines, supernatants removed from cells containing this gene activated the EGR1 assay. Thus, it is likely that this gene activates fibroblast cells through a signal transduction pathway. Early growth response 1 (EGR1) is a promoter associated with certain genes that induces various tissues and cell types upon activation, leading the cells to undergo differentiation and proliferation. The translation product of this gene shares sequence homology with murine claudin-1 and other murine and human members of the claudin family of integral membrane proteins which are structurally similar and contain four transmembrane domains (see, e.g., Genbank Acc. Nos. gi|3335182 (AF072127) and/or gi|4128015|gnl|PID|e1363658; all references available through these accessions are hereby incorporated in their entirety by reference herein). Three integral membrane proteins, claudin-1, -2, and occludin, are known to be components of tight junction (TJ) strands. FLAG-tagged claudin-1 and -2 protein have been demonstrated using immunofluorescence microscopy to be highly concentrated at cell contact sites as planes through a homophilic interaction. It is believed that claudin-1 and -2 are mainly responsible for TJ strand formation, and occludin is an accessory

protein in some function of TJ strands (see, e.g., J. Cell Biol 143:391-401 (1998), which is hereby incorporated by reference herein).

**[0069]** This gene is expressed primarily in wound healing tissues, and various carcinoma tissues, and, to a lesser extent, in some other tissues.

**[0070]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, tumorigenesis. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of wounded tissues, and cancerous tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0071]** The tissue distribution in healing wound tissue and various carcinomas indicates that polynucleotides and polypeptides corresponding to this gene would be useful for detection, diagnosis, treatment, and/or prevention of wounds and tumors. Representative uses are described elsewhere herein. Additionally, the homology of the translation product of this gene to claudin-1, a integral membrane protein involved in tight junction formation, and the biological activity of supernatants from cells expressing this gene on fibroblast cells in EGR assays indicate that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, diagnosis, treatment, and/or prevention of cancer and other proliferative disorders. Expression within cellular sources marked by proliferating cells (e.g., healing wound and various carcinomas) and the homology of the translation product of this gene to a family of claudin proteins indicates that this protein may play a role in the regulation of cellular division and tight junction formation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate

cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0072]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:17 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1242 of SEQ ID NO:17, b is an integer of 15 to 1256, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:17, and where b is greater than or equal to a + 14.

**[0073] FEATURES OF PROTEIN ENCODED BY GENE NO: 8**

**[0074]** The translation product of this gene shares sequence homology with fibulin which is thought to be important in cellular adhesion and extracellular matrix organization.

**[0075]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group:

GTRAGVSKYTGGRGVTWAPSSAAVPRISSATMRMGLTSFSTTGA (SEQ ID NO: 248),

WQSGHRLWQLEWPPPPLSADEHPWEGPLPGTSPSPKFSMPSPVPHGHRPTL  
TMTRSWRIFFNNIAYRSSSANRLFRVIRREHGDPLIEELNPGDALEPEGRGTGG  
VVTDFDGDGMLDLILSHGESMAQPLSVFRGNQGFNNNWLRVVPRTFRGAFA  
RGAKVVLYTKKSGAHLRIIDGGSGYLCMEPVAFHGLGKDEASSVEVTWPD  
GKMVSRNVASGEMNSVLEILYPRDEDTLQDPAPLECGQGFSQQENGHCMDT  
NECIQFPFVCPRDKPVCVNTYGSYRCRTNKKCSXGLRVPTRMAHTGL (SEQ  
ID NO: 249), WQSGHRLWQLEWPPPPLSADEHPWEGPLPGTSPSPK (SEQ ID

NO: 250), FSMSPVPHGHHRPTLTMTRSWRIFFNNIAYRSSS (SEQ ID NO: 251), ANRLFRVIRREHGDPLIEELNPGDALEPEGRGTGGVV (SEQ ID NO: 252), TDFDGDGMLDLILSHGESMAQPLSVFRGNQGFNN (SEQ ID NO: 253), NWLRVVPRTFRGAFARGAKVVLYTKKSGAHLRIID (SEQ ID NO: 254), GGSGYLCMEPVVAHFGLGKDEASSVEVTWPDGKMVS (SEQ ID NO: 255), RNVASGEMNSVLEILYPRDEDTLQDPAPLECGQGF (SEQ ID NO: 256), SQQENGHCMDTNECIQFPFVCPRDKPVCVNTYGSYR (SEQ ID NO: 257), and/or CRTNKKCSXGLRVPTRMAHTGL (SEQ ID NO: 258). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

[0076] The gene encoding the disclosed cDNA is believed to reside on chromosome 10. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 10.

[0077] This gene is expressed primarily in brain, kidney, Gessler Wilms tumor, and synovial sarcoma.

[0078] Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, thrombosis, atherosclerosis, neoplasia, schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease, transmissible spongiform encephalopathies (TSE), Creutzfeldt-Jakob disease (CJD), specific brain tumors, aphasia, mania, depression and dementia. Similarly, polypeptides and antibodies directed to these polypeptides would be useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous and cardiovascular systems, expression of this gene at significantly higher or lower levels may be



routinely detected in certain tissues or cell types (e.g., brain, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or cerebrospinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0079]** Based on the sequence similarity, the translation product of this clone is expected to share at least some biological activities with fibulin proteins. Such activities are known in the art, some of which are described elsewhere herein. Fibulin itself, can be used to manipulate adhesion of cells to fibronectin, collagen, laminin, and possibly also other proteins. The tissue distribution in brain and the homology to fibulin indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the treatment, prevention, detection and/or diagnosis of developmental, degenerative and/or neoplastic conditions (such as cancer) with mechanisms contingent on the regulation of cellular adhesion and extracellular matrix organization. Thrombosis, atherosclerosis and restenosis may be potential cardiovascular targets for application. In addition, polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or

receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0080]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:18 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1129 of SEQ ID NO:18, b is an integer of 15 to 1143, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:18, and where b is greater than or equal to a + 14.

#### **[0081] FEATURES OF PROTEIN ENCODED BY GENE NO: 9**

**[0082]** The translation product of this gene shares sequence homology with carbonic anhydrase VI, which is thought to be important in protein degradation and pH regulation (see, e.g., GenBank Accession No.: BAA78709.1 and Mori K, et al., J Biol Chem. 274:15701-5 (1999); EMBL locus BTCARANVI (accession X96503); and Jiang et al., Biochem. J. 318:291-296 (1996) which are hereby incorporated herein in their entireties, by reference). Based on this homology, it is likely that this gene would have activity similar to carbonic anhydrase.

**[0083]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group: QSPIDIQTD (SEQ ID NO: 259), LHNNGHTVQLSLPSTLYL (SEQ ID NO: 260), YVAAQLHLHWG (SEQ ID NO: 261), AELHIVHYDSD (SEQ ID NO: 262), GQHWTYEGPHGQDHWP (SEQ ID NO: 263), QSPIDIQTDSVTFD (SEQ ID NO: 264), LHNNGHTVQLSLPST (SEQ ID NO: 265), KYVAAQLHLHWG (SEQ ID NO: 266), and/or AELHIVHYDSDSY (SEQ ID NO: 267). Moreover, fragments and

variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0084]** The gene encoding the disclosed cDNA is thought to reside on chromosome 1. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 1.

**[0085]** This gene is expressed primarily in fetal tissues and brain tissue, and, to a lesser extent, in melanocytes, wilms tumor and retinal tissues.

**[0086]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, glaucoma and alkalosis resulting from disease of the kidney. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the systems regulating ionic balance and pH in the fluids of the body, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., metabolic, regulatory, renal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one, two, three, four, five, six or all seven of the immunogenic epitopes shown in SEQ ID NO: 126 as residues: Tyr-24 to His-32, Pro-38 to Ala-44, Pro-66 to Glu-75, His-111 to Gly-116, Tyr-139 to Ser-146, Thr-176 to Ser-181, Lys-239 to Lys-249.

Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

[0087] The tissue distribution and homology to secreted carbonic anhydrase indicates that polynucleotides and polypeptides corresponding to this gene would be useful for developing drugs that modulate ionic balance in the serum and in the retina, and may be used for treating diseases such as glaucoma or alkalosis secondary to renal disease. Representative uses are described elsewhere herein. Furthermore, this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Alternatively, this gene product may be involved in the pattern of cellular proliferation that accompanies early embryogenesis. Thus, aberrant expression of this gene product in tissues - particularly adult tissues - may correlate with patterns of abnormal cellular proliferation, such as found in various cancers. Because of potential roles in proliferation and differentiation, polynucleotides and polypeptides corresponding to this gene may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention would be useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. Polynucleotides and polypeptides corresponding to this gene would be useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. Polynucleotides and polypeptides of the invention can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological

activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. The protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[0088] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:19 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1523 of SEQ ID NO:19, b is an integer of 15 to 1537, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:19, and where b is greater than or equal to a + 14.

#### **[0089] FEATURES OF PROTEIN ENCODED BY GENE NO: 10**

[0090] The translation product of this gene shares sequence homology with murine CD63/ME491 which is thought to be important in activation of macrophage and platelet population (marker of); CD37 (Genbank Acc. No. gi|29794, all references available through this accession are hereby incorporated in their entirety by reference herein), a human leukocyte marker; and several members of the tetraspanin protein family (see, e.g., Genbank Acc. No. gi|3152703 (AF065389) and gi|2995865 (AF053455) , all references available through these accessions are hereby incorporated in their entirety by reference herein), which are expressed in a wide

variety of species and regulate cell adhesion, migration, proliferation and differentiation.

[0091] This translation product of this gene appears to contain four transmembrane domains starting from about amino acid positions 24 to about 40, from about 98 to about 114, from about position 62 to about 78, from about position 235 to about 251. Further, this polypeptide is likely to be a Type IIIa membrane protein (Ncyt Cexo) as identified using the PSORT analysis tool. The transmembrane 4 superfamily (TM4SF) which has at least 16 members is the second biggest subfamily among CD antigen superfamilies and activation antigens of T-cells. All TM4SF members contain four putative transmembrane domains, two extracellular loops, and two short cytoplasmic tails. They are variously expressed on immature, early, mature, activated lymphocytes, monocytes, macrophages, granulocytes, platelets, eosinophils, basophils, certain leukemic and lymphoma cells, and a variety of other cells and tissues. CD9 cell surface protein is expressed by both hematopoietic and neural cells, and may play a role in intercellular signaling in the immune and nervous system. CD63 is a 53-Kd lysosomal membrane glycoprotein that has been identified as a platelet activation molecule; it plays an important role in cell adhesion of platelets and endothelial cells. Increased mRNA for CD63 antigen was found in atherosclerotic lesions of Watanabe heritable hyperlipidemic rabbits, suggesting a potential role of CD63 in progression of atherosclerosis. CD63 is also a mast cell marker. This gene also shares close homology with C33 antigen (CD82); CD82 was originally identified as the target of several mAbs inhibitory to syncytium formation induced by human T-cell leukemia virus type I (HTLV-I), the etiological agent of adult T-cell leukemia. Therefore, this gene could be a target for the development of a drug for this leukemia. CD81 is the target of an antiproliferative antibody. A diverse group of human cell lines, including hematology, neuroectodermal, and mesenchymal cells, express the CD81 protein. Many of the lymphoid cell lines, in particular those derived from large cell lymphomas, were susceptible to the antiproliferative effects of the antibody. CD81 may therefore play an important role in the regulation of lymphoma cell growth. CD9, CD20, CD37, CD63, CD81 and CD82 have been implicated in the regulation of cell growth, adhesion, and signal transduction of B, T lymphocytes and

some other non-lymphoid cells. They associate with CD2, CD21, CD4, CD8, MHC Class II molecules, integrins, and function as co-receptor for T, B and other lymphoid cells. Some TM4SF are leukocyte antigens, highly expressed in activated leukocytes, lymphocytes, and are highly specific surface markers for lymphoblastic leukemia, lymphoma, melanoma, and neuroblastoma. CD9 has been shown to be involved in cell motility and tumor metastasis. These antigens could be a valuable immunogen or target to implement active and passive immunotherapy in patients with cancer. Others have been shown to be involved in inhibition of prostate cancer metastasis.

[0092] In specific embodiments, polynucleotides of the invention comprise, or alternatively consist of, the following nucleotide sequence:

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GGCCGCGCCGCGCTGCCGCGCCGCGCGGATTCTGCTTCTCAGAAGAT
GCACTATTATAGATACTCTAACGCCAAGGTCAGCTGCTGGTACAAGTACC
TCCTTTTCAGCTACAACATCATCTTCTGATTGGCTGGAGTTGTCTTCCTTGG
AGTCGGGCTGTGGGCATGGAGCGAAAAGGGTGTGCTGTCCGACCTCACCA
AAGTGACCCGGATGCATGGAATCGACCCTGTGGTGCTGGTCCTGATGGTG
GGCGTGCTGATGTTACCCCTGGGGTTCGCCGGCTGCGTGGGGGCTCTGCG
GGAGAATATCTGCTTGCTCAACTTTTTCTGTGGCACCATCGTGCTCATCTT
CTTCCTGGAGCTGGCTGTGGCCGTGCTGGCCTTCCTGTTCCAGGACTGGGT
GAGGGACCGGTTCCGGGAGTTCTTCGAGAGCAACATCAAGTCCTACCGGG
ACGATATCGATCTGCAAAACCTCATCGACTCCCTTCAGAAAGCTAACCAG
TGCTGTGGCGCATATGGCCCTGAAAGACTGGGACCTCAGACGTCTACTTC
AATTGCAGCGGTGCCAGCTACAGCCGAGAGAATGCGGGGTCCCCTTCTCC
TGCTGCGTGCCAGATCCTGCGCAAAAAGTTGTGAACACACAGTGTGGATA
TGATGTCAGGATTGAGCTGAAGAGCAAGTGGGATGAGTCCATCTTCACGA
AAGGCTGCATCCAGGCGCTGGAAAGCTGGCTCCCGCGGAACATTTACATT
GTGGCTGGCGTCTTCATCGCCATCTCGCTGTTGCAGATATTTGGCATCTTC
CTGGCAAGGACGCTGATCTCAGACATCGAGGCAGTGAAGGCCGGCCATCA
CTTCTGAGGAGCAGAGTTGAGGGAGCCGAGCTGAGCCACGCTGGGAGGC
CAGAGCCTTTCTCTGCCATCAGCCCTACGTCCAGAGGGAGAGGAGCCGAC
ACCCCCAGAGCCAGTGCCCCATCTTAAGCATCAGCGTGACGTGACCTCTC
TGTTTCTGCTTGCTGGTGCTGAAGACCAAGGGTCCCCCTTGTTACCTGCCC

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AAACTTGTGACTGCATCCCTCTGGAGTCTACCCAGAGACAGAGAATGTGT  
CTTTATGTGGGAGTGGTGACTCTGAAAGACAGAGAGGGCTCCTGTGGCTG  
CCAGGAGGGCTTGACTCAGACCCCCTGCAGCTCAAGCATGTCTGCAGGAC  
ACCTGGTCCCCCTCTCCCAGTGGCATCCCAAACATCTGCTTTGGGTCCATC  
CCACATCTGTGGGTGGGCCCCGTGGGTAAAGAAGGGAACCCACAGGCGTG  
GAACAGGGCATCCTCTCTCCCATCCAAGCAAAGCCAGCATGGGGGCCTGC  
CCGTAACGGGAGGCGGACGTGGCCCCGCTGGGCCTCTGAGTGCCAGCGCA  
GTCTGCTGGGACATGCACATATCAGGGGTTGTTTGCAGGATCCTCAGCCA  
TGTTCAAGTGAAGTAAGCCTGAGCCAGTGCGTGGACTGGTGCCACGGGAG  
TGCTTGTCCACTGTCCCCCTGTGTCCACCAGCTATTCTCCTGGCGCCGGA  
ACTGCCTCTGGTCTTGATAGCATTAAGCCCTGATTGGCCGGTGGCGCGGTG  
GGCATGGTTCTTCACTGAGAGCCGGCTCTCCTTTTCTTAAAGTGTGTAAAT  
AGTTTATTT (SEQ ID NO:268). In specific embodiments, polypeptides of the

invention comprise, or alternatively consist of, the following amino acid sequence:

MHYRYRNAKVSCWYKYLFSYNIIFWLAGVVFLGVGLWAWSEKGVLSDL  
TKVTRMHGIDPVVLVLMVGVVMFTLGFAGCVGALRENICLLNFFCGTIVLIFF  
LELAVAVLAFLFQDWVRDRFREFFESNIKSyrDDIDLQNLIDSLQKANQCCGA  
YGPEDWDLNVYFNCSGASYSREKCGVPFSCVDPAPQKVNTQCGYDVRIQ  
LKSKWDESIFTKGCIQALESWLPRNIYIVAGVFIAISLLQIFGIFLARTLISDIEAV

KAGHHF (SEQ ID NO: 269) Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0093]** This gene maps to chromosome 10, and therefore would be useful in linkage analysis as a marker for chromosome 10.

**[0094]** This gene is expressed primarily in infant and human brain and, to a lesser extent, in pancreas islet cell tumor, Wilm's tumor, uterine cancer, and B cell lymphomas.



**[0095]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions: cancers and central nervous system disorders. Similarly, polypeptides and antibodies directed to those polypeptides would be useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the, immune, metabolic and central nervous system, expression of this gene at significantly higher or lower levels may be detected in certain tissues or cell types (e.g., CNS, cancerous and wounded tissues) or bodily fluids (e.g., lymph, bile, serum, plasma, urine, synovial fluid or spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of the immunogenic epitopes shown in SEQ ID NO: 127 as residues: Met-1 to Ala-9. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0096]** The tissue distribution in infant and human brain, and various tumors, and homology to murine CD63/ME491, human CD37, and tetraspanins indicates that polynucleotides and/or polypeptides corresponding to this gene would be useful for the study, detection, treatment, and/or prevention of central nervous system diseases and cancers. Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells, and its homology indicates that polynucleotides and/or polypeptides of the invention may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain

neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention would be useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The polynucleotides and/or polypeptides of the invention would be useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[0097] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:20 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2658 of SEQ ID NO:20, b is an integer of 15 to 2672, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:20, and where b is greater than or equal to a + 14.

#### **[0098] FEATURES OF PROTEIN ENCODED BY GENE NO: 11**

[0099] In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group:

SQLLPGSVPGWAAHPLRRTVLSPSQHTHNSSHRMKANCEVSASQRLTGRI RH  
PRGLLQNSPRSRKLWMRLGLRSRYSGTQARSAPAGGHIVDTAEQRQVQARV  
PWAAAVARQLLRYEKAKASAGTPPAHKPCCHYRCCGYSQAQQKPTASAPQ  
HLYRPTRPHFRGCRSISV (SEQ ID NO: 279),

SGNLGSADGWAYIDVEVRRPWAFVGP GCSRSSGNGSTAYGLVGSPRWLSPF  
HTGGAVSLPRRPRGPGPVLGVARPCLRCVLRPEHYEPGSHYSGFAGRDASRA  
FVTGDCSEAGLVDDVSDLSAAEMLTLHNWLSFYEKNYVCVGRVTGRFYGED  
GLPTPALTQVEAAITRGLEANKLQLQEKQTFPPCNAEWSSARG SRLWCSQKS  
GGVSRDWIGVPRKLYKPGAKEPRCVCVRTTGPPSGQMPDNPPHRNRGDL DH  
PNLAEYTGCPPLAITCSFPL (SEQ ID NO: 270),

SGNLGSADGWAYIDVEVRRPWAFVGP GCSRSSGNGS (SEQ ID NO: 271),

TAYGLVGSPRWLSPFHTGGAVSLPRRPRGPGPVLGV (SEQ ID NO: 272),

ARPCVLRPEHYEPGSHYSGFAGRDASRA FVTGD (SEQ ID NO: 273),

CSEAGLVDDVSDLSAAEMLTLHNWLSFYEKNYVCVG (SEQ ID NO: 274),

RVTGRFYGEDGLPTPALTQVEAAITRGLEANKLQLQ (SEQ ID NO: 275),

EKQTFPPCNAEWSSARG SRLWCSQKSGGVSRDWIGV (SEQ ID NO: 276),

PRKLYKPGAKEPRCVCVRTTGPPSGQMPD (SEQ ID NO: 277), and/or

NPPHRNRGDL DHPNLAEYTGCPPLAITCSFPL (SEQ ID NO: 278). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

[0100] The translation product of this gene shares sequence homology to several steroid receptor proteins (see, e.g., Genbank Acc. Nos. gnl|PID|e314174, gnl|PID|e1154367 (AJ002030), and/or gnl|PID|e257707); all references available through these accessions are hereby incorporated by reference herein). Based on the

sequence similarity, the translation product of this clone is expected to share at least some biological activities with steroid receptor binding proteins. Such activities are known in the art, some of which are described elsewhere herein.

**[0101]** This gene is expressed primarily in brain, fetal tissue, immune cells (e.g., T-cells), breasts and, to a lesser extent, in variety of other tissues and cell types.

**[0102]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental, degenerative and behavioral diseases of the brain such as schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease, transmissible spongiform encephalopathies (TSE), Creutzfeldt-Jakob disease (CJD), specific brain tumors, aphasia, mania, depression, dementia, paranoia, addictive behavior and sleep disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one, two or all three of the immunogenic epitopes shown in SEQ ID NO: 128 as residues: Glu-42 to Pro-53, Ser-67 to Thr-73, Ala-84 to Leu-90. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0103]** The tissue distribution in brain and the homology to steroid receptor proteins indicates polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in

Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, transmissible spongiform encephalopathy (TSE), Creutzfeldt-Jakob disease (CJD), aphasia, specific brain tumors, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. The tissue distribution in T-cells indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis, detection, prevention, and/or treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. Involvement in the regulation of cytokine production, antigen presentation, or other processes indicates a usefulness for treatment of cancer (e.g., by boosting immune responses). Expression in cells of lymphoid origin, indicates the natural gene product would be involved in immune functions. Therefore it would also be useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's

disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0104]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:21 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1494 of SEQ ID NO:21, b is an integer of 15 to 1508, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:21, and where b is greater than or equal to a + 14.

**[0105] FEATURES OF PROTEIN ENCODED BY GENE NO: 12**

**[0106]** The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 144-160 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 161-222 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ia membrane proteins.

**[0107]** This gene is expressed primarily in kidney and gall bladder tissues, fetal tissue, and testes tissue.

[0108] Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, renal disorders, metabolic diseases, and disorders of the reproductive and developing organs. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the renal, metabolic, developing, and reproductive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., renal, metabolic, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of the immunogenic epitopes shown in SEQ ID NO: 129 as residues: Lys-60 to Ala-66. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

[0109] The tissue distribution in kidney and gall bladder tissues, testicular tissue, and fetal tissues, indicates that polynucleotides and polypeptides corresponding to this gene would be useful for treatment, prevention, detection and/or diagnosis of disorders of the renal system, reproductive system, metabolic system and developing systems. Furthermore, the tissue distribution in kidney indicates that polynucleotides and polypeptides corresponding to this gene would be useful in the treatment, prevention, diagnosis and/or detection of kidney diseases including renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilm's Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Alternatively, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the treatment and

diagnosis of conditions concerning proper testicular function (e.g., endocrine function, sperm maturation), as well as cancer. Therefore, this gene product would be useful in the treatment of male infertility and/or impotence. This gene product is also useful in assays designed to identify binding agents, as such agents (antagonists) would be useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, this gene product may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[0110] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:22 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1433 of SEQ ID NO:22, b is an integer of 15 to 1447, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:22, and where b is greater than or equal to a + 14.

#### **[0111] FEATURES OF PROTEIN ENCODED BY GENE NO: 13**

[0112] The translation product of this gene shares weak homology with O-linked GlcNAc transferases (see, e.g., Genbank Acc. No. gi|2266994) which are important for a variety of cellular functions, including, but not limited to, stability of secreted proteins and proper function. Based on the sequence similarity, the translation product of this clone is expected to share at least some biological activities with glycosylation



enzyme proteins. Such activities are known in the art, (see, e.g., G Lubas WA, et al., J Biol Chem. 272:9316-24 (1997); all references available through this citation are hereby incorporated herein by reference) and some of which are described elsewhere herein.

[0113] In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group:

LLLCPPWWLCFDWS (SEQ ID NO: 280),

MGCIPLIKSISDWRVIALAALWFCLIGLICQALCSEDGHKRRILTLGLGFLVIPF  
LPASNLFVRVGFVVAECVLYLPSIGYCVLLTFGFGALSKHTKKKKLIAAVVLG  
ILFINTLRCVLRRTAKWRSEEQLFRSALSVCPLNAKVHYNIGKNLADKGNQTA  
AIRYYREAVRLNPKYVHAMNNLGNILKERNELQEAELLASLAVQIQPDFAAA  
WMNLGIVQNSLKRFEAEQNYRTAIKHRRKYPDCYYNLGRLVRTGCPVPVE  
GKMGYFS (SEQ ID NO: 281),

MGCIPLIKSISDWRVIALAALWFCLIGLICQALCSEDG (SEQ ID NO: 282),

HKRRILTLGLGFLVIPFLPASNLFFRVGFVVAECVLYL (SEQ ID NO: 283),

PSIGYCVLLTFGFGALSKHTKKKKLIAAVVLGILFINT (SEQ ID NO: 284),

LRCVLRRTAKWRSEEQLFRSALSVCPLNAKVHYNIGKNL (SEQ ID NO: 285),

ADKGNQTAIRYYREAVRLNPKYVHAMNNLGNILKERN (SEQ ID NO: 286),

ELQEAELLASLAVQIQPDFAAAWMNLGIVQNSLKRFE (SEQ ID NO: 287),

and/or AEQNYRTAIKHRRKYPDCYYNLGRLVRTGCPVPVEGKMGYFS (SEQ

ID NO: 288). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention.

Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

[0114] The polypeptide encoded by this gene has been determined to have transmembrane domains at about amino acid position 38 to about 54, at about 136 to about 152, at about 161 to about 177, at about 192 to about 208, at about 223 to about 239, at about 243 to about 259, at about 374 to about 390, at about 402 to about 418,

at about 432 to about 448, and at about 461 to about 477 of the amino acid sequence referenced in Table 7 for this gene. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type IIIa membrane proteins.

[0115] Included in this invention as preferred domains are Aldo/keto reductase family putative active site signatures, which were identified using the ProSite analysis tool (Swiss Institute of Bioinformatics). The aldo-keto reductase family groups together a number of structurally and functionally related NADPH-dependent oxidoreductases as well as some other proteins. Three consensus patterns specific to this family of proteins were developed. The third pattern, located in the C-terminal, is centered on a lysine residue whose chemical modification, in aldose and aldehyde reductases, affect the catalytic efficiency. The consensus pattern is as follows: [LIVM]-[PAIV]-[KR]-[ST]-x(4)-R-x(2)-[GSTAEQK]-[NSL]-x(2)-[LIVMFA] [K is a putative active site residue]. In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence: LIKSISDWRVIALAAL (SEQ ID NO: 289). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention. Further preferred are polypeptides comprising the Aldo/keto reductase family putative active site signature above, and at least 5, 10, 15, 20, 25, 30, 50, or 75 additional contiguous amino acid residues of the amino acid sequence referenced in Table 7 for this gene. The additional contiguous amino acid residues may be N-terminal or C-terminal to the Aldo/keto reductase family putative active site signatures. Alternatively, the additional contiguous amino acid residues may be both N-terminal and C-terminal to the Aldo/keto reductase family putative active site signatures, wherein the total N- and C-terminal contiguous amino acid residues equal the specified number.

[0116] Figures 1A-G show the nucleotide (SEQ ID NO:23) and deduced amino acid sequence (SEQ ID NO: 130) corresponding to this gene.

[0117] Figure 2 shows an analysis of the amino acid sequence (SEQ ID NO: 130). Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown, and all were generated using the default settings of the recited computer algorithms. In the "Antigenic Index or Jameson-Wolf" graph, the positive peaks indicate locations of the highly antigenic regions of the protein, i.e., regions from which epitope-bearing peptides of the invention can be obtained. Polypeptides comprising, or alternatively consisting of, domains defined by these graphs are contemplated by the present invention, as are polynucleotides encoding these polypeptides.

[0118] The data presented in Figure 2 are also represented in tabular form in Table 3. The columns are labeled with the headings "Res", "Position", and Roman Numerals I-XIV. The column headings refer to the following features of the amino acid sequence presented in Figure 2, and Table 3: "Res": amino acid residue of SEQ ID NO: 130 and Figures 1A-G; "Position": position of the corresponding residue within SEQ ID NO: 130 and Figures 1A-G; I: Alpha, Regions - Garnier-Robson; II: Alpha, Regions - Chou-Fasman; III: Beta, Regions - Garnier-Robson; IV: Beta, Regions - Chou-Fasman; V: Turn, Regions - Garnier-Robson; VI: Turn, Regions - Chou-Fasman; VII: Coil, Regions - Garnier-Robson; VIII: Hydrophilicity Plot - Kyte-Doolittle; IX: Hydrophobicity Plot - Hopp-Woods; X: Alpha, Amphipathic Regions - Eisenberg; XI: Beta, Amphipathic Regions - Eisenberg; XII: Flexible Regions - Karplus-Schulz; XIII: Antigenic Index - Jameson-Wolf; and XIV: Surface Probability Plot - Emini.

[0119] Preferred embodiments of the invention in this regard include fragments that comprise, or alternatively consisting of, one or more of the following regions: alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet forming regions ("beta-regions"), turn and turn-forming regions ("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions, surface-forming regions and high antigenic index regions. The data representing the structural

or functional attributes of the protein set forth in Figure 2 and/or Table 3, as described above, was generated using the various modules and algorithms of the DNA\*STAR set on default parameters. In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Table 3 can be used to determine regions of the protein which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or XIV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

[0120] Certain preferred regions in these regards are set out in Figure 2, but may, as shown in Table 3, be represented or identified by using tabular representations of the data presented in Figure 2. The DNA\*STAR computer algorithm used to generate Figure 2 (set on the original default parameters) was used to present the data in Figure 2 in a tabular format (See Table 3). The tabular format of the data in Figure 2 is used to easily determine specific boundaries of a preferred region.

[0121] The present invention is further directed to fragments of the polynucleotide sequences described herein. By a fragment of, for example, the polynucleotide sequence of a deposited cDNA or the nucleotide sequence shown in SEQ ID NO:23, is intended polynucleotide fragments at least about 15nt, and more preferably at least about 20 nt, at least about 25nt, still more preferably at least about 30 nt, at least about 35nt, and even more preferably, at least about 40 nt in length, at least about 45nt in length, at least about 50nt in length, at least about 60nt in length, at least about 70nt in length, at least about 80nt in length, at least about 90nt in length, at least about 100nt in length, at least about 125nt in length, at least about 150nt in length, at least about 175nt in length, which are useful as diagnostic probes and primers as discussed herein. Of course, larger fragments 200-1500 nt in length are also useful according to the present invention, as are fragments corresponding to most, if not all, of the nucleotide sequence of a deposited cDNA or as shown in SEQ ID NO:23. By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases from the nucleotide sequence of a deposited cDNA or the nucleotide sequence as shown in SEQ ID NO:23. In this context "about" includes the

particularly recited size, an sizes larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Representative examples of polynucleotide fragments of the invention include, for example, fragments that comprise, or alternatively, consist of, a sequence from about nucleotide 1 to about 50, from about 51 to about 100, from about 101 to about 150, from about 151 to about 200, from about 201 to about 250, from about 251 to about 300, from about 301 to about 350, from about 351 to about 400, from about 401 to about 450, from about 451 to about 500, and from about 501 to about 550, and from about 551 to about 600, from about 601 to about 650, from about 651 to about 700, from about 701 to about 750, from about 751 to about 800, from about 801 to about 850, from about 851 to about 900, from about 901 to about 950, from about 951 to about 1000, from about 1001 to about 1050, from about 1051 to about 1100, from about 1101 to about 1150 from about 1151 to about 1200, from about 1201 to about 1250, from about 1251 to about 1300, from about 1301 to about 1350, from about 1351 to about 1400, from about 1401 to about 1450, from about 1451 to about 1500, from about 1501 to about 1550, from about 1551 to about 1600, from about 1601 to about 1650, from about 1651 to about 1700, from about 1701 to about 1750, from about 1751 to about 1800, from about 1801 to about 1850, from about 1851 to about 1900, from about 1901 to about 1950, from about 1951 to about 2000, from about 2001 to about 2050, from about 2051 to about 2100, from about 2101 to about 2150 from about 2151 to about 2200, from about 2201 to about 2250, from about 2251 to about 2300, from about 2301 to about 2350, from about 2351 to about 2400, from about 2401 to about 2450, from about 2451 to about 2500, 2501 to about 2550, from about 2551 to about 2600, from about 2601 to about 2650, from about 2651 to about 2700, from about 2701 to about 2750, from about 2751 to about 2800, from about 2801 to about 2850, from about 2851 to about 2900, from about 2901 to about 2950, from about 2951 to about 3000, from about 3001 to about 3050, from about 3051 to about 3100, from about 3101 to about 3150 from about 3151 to about 3200, from about 3201 to about 3250, from about 3251 to about 3300, from about 3301 to about 3350, from about 3351 to about 3400, from about 3401 to about 3450, from about 3451 to about 3500, 3501 to about 3550, from about 3551 to about 3600, from about 3601 to about 3650, from

about 3651 to about 3700, from about 3701 to about 3750, from about 3751 to about 3800, from about 3801 to about 3850, and from about 3851 to 3886 of SEQ ID NO:23, or the complementary strand thereto, or the cDNA contained in a deposited clone. In this context "about" includes the particularly recited ranges, and ranges larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. In additional embodiments, the polynucleotides of the invention encode functional attributes of the corresponding protein.

**[0122]** Preferred polypeptide fragments of the invention comprise, or alternatively consist of, the secreted protein having a continuous series of deleted residues from the amino or the carboxy terminus, or both. Particularly, N-terminal deletions of the polypeptide can be described by the general formula m-760 where m is an integer from 2 to 755, where m corresponds to the position of the amino acid residue identified in SEQ ID NO:130. More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, an amino acid sequence selected from the group: I-2 to V-760; P-3 to V-760; N-4 to V-760; Q-5 to V-760; H-6 to V-760; N-7 to V-760; A-8 to V-760; G-9 to V-760; A-10 to V-760; G-11 to V-760; S-12 to V-760; H-13 to V-760; Q-14 to V-760; P-15 to V-760; A-16 to V-760; V-17 to V-760; F-18 to V-760; R-19 to V-760; M-20 to V-760; A-21 to V-760; V-22 to V-760; L-23 to V-760; D-24 to V-760; T-25 to V-760; D-26 to V-760; L-27 to V-760; D-28 to V-760; H-29 to V-760; I-30 to V-760; L-31 to V-760; P-32 to V-760; S-33 to V-760; S-34 to V-760; V-35 to V-760; L-36 to V-760; P-37 to V-760; P-38 to V-760; F-39 to V-760; W-40 to V-760; A-41 to V-760; K-42 to V-760; L-43 to V-760; V-44 to V-760; V-45 to V-760; G-46 to V-760; S-47 to V-760; V-48 to V-760; A-49 to V-760; I-50 to V-760; V-51 to V-760; C-52 to V-760; F-53 to V-760; A-54 to V-760; R-55 to V-760; S-56 to V-760; Y-57 to V-760; D-58 to V-760; G-59 to V-760; D-60 to V-760; F-61 to V-760; V-62 to V-760; F-63 to V-760; D-64 to V-760; D-65 to V-760; S-66 to V-760; E-67 to V-760; A-68 to V-760; I-69 to V-760; V-70 to V-760; N-71 to V-760; N-72 to V-760; K-73 to V-760; D-74 to V-760; L-75 to V-760; Q-76 to V-760; A-77 to V-760; E-78 to V-760; T-79 to V-760; P-80 to V-760; L-81 to V-760; G-82 to V-760; D-83 to V-760; L-84 to V-760; W-85 to V-760; H-86 to V-760; H-87 to V-760; D-88 to V-760; F-89 to V-760; W-90

to V-760; G-91 to V-760; S-92 to V-760; R-93 to V-760; L-94 to V-760; S-95 to V-760; S-96 to V-760; N-97 to V-760; T-98 to V-760; S-99 to V-760; H-100 to V-760; K-101 to V-760; S-102 to V-760; Y-103 to V-760; R-104 to V-760; P-105 to V-760; L-106 to V-760; T-107 to V-760; V-108 to V-760; L-109 to V-760; T-110 to V-760; F-111 to V-760; R-112 to V-760; I-113 to V-760; N-114 to V-760; Y-115 to V-760; Y-116 to V-760; L-117 to V-760; S-118 to V-760; G-119 to V-760; G-120 to V-760; F-121 to V-760; H-122 to V-760; P-123 to V-760; V-124 to V-760; G-125 to V-760; F-126 to V-760; H-127 to V-760; V-128 to V-760; V-129 to V-760; N-130 to V-760; I-131 to V-760; L-132 to V-760; L-133 to V-760; H-134 to V-760; S-135 to V-760; G-136 to V-760; I-137 to V-760; S-138 to V-760; V-139 to V-760; L-140 to V-760; M-141 to V-760; V-142 to V-760; D-143 to V-760; V-144 to V-760; F-145 to V-760; S-146 to V-760; V-147 to V-760; L-148 to V-760; F-149 to V-760; G-150 to V-760; G-151 to V-760; L-152 to V-760; Q-153 to V-760; Y-154 to V-760; T-155 to V-760; S-156 to V-760; K-157 to V-760; G-158 to V-760; R-159 to V-760; R-160 to V-760; L-161 to V-760; H-162 to V-760; L-163 to V-760; A-164 to V-760; P-165 to V-760; R-166 to V-760; A-167 to V-760; S-168 to V-760; L-169 to V-760; L-170 to V-760; A-171 to V-760; A-172 to V-760; L-173 to V-760; L-174 to V-760; F-175 to V-760; A-176 to V-760; V-177 to V-760; H-178 to V-760; P-179 to V-760; V-180 to V-760; H-181 to V-760; T-182 to V-760; E-183 to V-760; C-184 to V-760; V-185 to V-760; A-186 to V-760; G-187 to V-760; V-188 to V-760; V-189 to V-760; G-190 to V-760; R-191 to V-760; A-192 to V-760; D-193 to V-760; L-194 to V-760; L-195 to V-760; C-196 to V-760; A-197 to V-760; L-198 to V-760; F-199 to V-760; F-200 to V-760; L-201 to V-760; L-202 to V-760; S-203 to V-760; F-204 to V-760; L-205 to V-760; G-206 to V-760; Y-207 to V-760; C-208 to V-760; K-209 to V-760; A-210 to V-760; F-211 to V-760; R-212 to V-760; E-213 to V-760; S-214 to V-760; N-215 to V-760; K-216 to V-760; E-217 to V-760; G-218 to V-760; A-219 to V-760; H-220 to V-760; S-221 to V-760; S-222 to V-760; T-223 to V-760; F-224 to V-760; W-225 to V-760; V-226 to V-760; L-227 to V-760; L-228 to V-760; S-229 to V-760; I-230 to V-760; F-231 to V-760; L-232 to V-760; G-233 to V-760; A-234 to V-760; V-235 to V-760; A-236 to V-760; M-237 to V-760; L-238 to V-760; C-239 to V-760; K-240 to V-760; E-241 to V-760; Q-242 to V-760; G-243 to V-760; I-244 to V-760; T-245 to V-760;

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E-556 to V-760; L-557 to V-760; L-558 to V-760; S-559 to V-760; L-560 to V-760; A-561 to V-760; V-562 to V-760; Q-563 to V-760; I-564 to V-760; Q-565 to V-760; P-566 to V-760; D-567 to V-760; F-568 to V-760; A-569 to V-760; A-570 to V-760; A-571 to V-760; W-572 to V-760; M-573 to V-760; N-574 to V-760; L-575 to V-760; G-576 to V-760; I-577 to V-760; V-578 to V-760; Q-579 to V-760; N-580 to V-760; S-581 to V-760; L-582 to V-760; K-583 to V-760; R-584 to V-760; F-585 to V-760; E-586 to V-760; A-587 to V-760; A-588 to V-760; E-589 to V-760; Q-590 to V-760; S-591 to V-760; Y-592 to V-760; R-593 to V-760; T-594 to V-760; A-595 to V-760; I-596 to V-760; K-597 to V-760; H-598 to V-760; R-599 to V-760; R-600 to V-760; K-601 to V-760; Y-602 to V-760; P-603 to V-760; D-604 to V-760; C-605 to V-760; Y-606 to V-760; Y-607 to V-760; N-608 to V-760; L-609 to V-760; G-610 to V-760; R-611 to V-760; L-612 to V-760; Y-613 to V-760; A-614 to V-760; D-615 to V-760; L-616 to V-760; N-617 to V-760; R-618 to V-760; H-619 to V-760; V-620 to V-760; D-621 to V-760; A-622 to V-760; L-623 to V-760; N-624 to V-760; A-625 to V-760; W-626 to V-760; R-627 to V-760; N-628 to V-760; A-629 to V-760; T-630 to V-760; V-631 to V-760; L-632 to V-760; K-633 to V-760; P-634 to V-760; E-635 to V-760; H-636 to V-760; S-637 to V-760; L-638 to V-760; A-639 to V-760; W-640 to V-760; N-641 to V-760; N-642 to V-760; M-643 to V-760; I-644 to V-760; I-645 to V-760; L-646 to V-760; L-647 to V-760; D-648 to V-760; N-649 to V-760; T-650 to V-760; G-651 to V-760; N-652 to V-760; L-653 to V-760; A-654 to V-760; Q-655 to V-760; A-656 to V-760; E-657 to V-760; A-658 to V-760; V-659 to V-760; G-660 to V-760; R-661 to V-760; E-662 to V-760; A-663 to V-760; L-664 to V-760; E-665 to V-760; L-666 to V-760; I-667 to V-760; P-668 to V-760; N-669 to V-760; D-670 to V-760; H-671 to V-760; S-672 to V-760; L-673 to V-760; M-674 to V-760; F-675 to V-760; S-676 to V-760; L-677 to V-760; A-678 to V-760; N-679 to V-760; V-680 to V-760; L-681 to V-760; G-682 to V-760; K-683 to V-760; S-684 to V-760; Q-685 to V-760; K-686 to V-760; Y-687 to V-760; K-688 to V-760; E-689 to V-760; S-690 to V-760; E-691 to V-760; A-692 to V-760; L-693 to V-760; F-694 to V-760; L-695 to V-760; K-696 to V-760; A-697 to V-760; I-698 to V-760; K-699 to V-760; A-700 to V-760; N-701 to V-760; P-702 to V-760; N-703 to V-760; A-704 to V-760; A-705 to V-760; S-706 to V-760; Y-707 to V-760; H-708 to V-760; G-709 to V-760; N-710 to

V-760; L-711 to V-760; A-712 to V-760; V-713 to V-760; L-714 to V-760; Y-715 to V-760; H-716 to V-760; R-717 to V-760; W-718 to V-760; G-719 to V-760; H-720 to V-760; L-721 to V-760; D-722 to V-760; L-723 to V-760; A-724 to V-760; K-725 to V-760; K-726 to V-760; H-727 to V-760; Y-728 to V-760; E-729 to V-760; I-730 to V-760; S-731 to V-760; L-732 to V-760; Q-733 to V-760; L-734 to V-760; D-735 to V-760; P-736 to V-760; T-737 to V-760; A-738 to V-760; S-739 to V-760; G-740 to V-760; T-741 to V-760; K-742 to V-760; E-743 to V-760; N-744 to V-760; Y-745 to V-760; G-746 to V-760; L-747 to V-760; L-748 to V-760; R-749 to V-760; R-750 to V-760; K-751 to V-760; L-752 to V-760; E-753 to V-760; L-754 to V-760; and M-755 to V-760 of SEQ ID NO:130. Polypeptides encoded by these polynucleotides are also encompassed by the invention.

**[0123]** Also as mentioned above, even if deletion of one or more amino acids from the C-terminus of a protein results in modification or loss of one or more biological functions of the protein, other functional activities (e.g., biological activities, ability to multimerize, ability to bind ligand, ability to generate antibodies, ability to bind antibodies) may still be retained. For example the ability of the shortened polypeptide to induce and/or bind to antibodies which recognize the complete or mature forms of the polypeptide generally will be retained when less than the majority of the residues of the complete or mature polypeptide are removed from the C-terminus. Whether a particular polypeptide lacking C-terminal residues of a complete polypeptide retains such immunologic activities can readily be determined by routine methods described herein and otherwise known in the art. It is not unlikely that a polypeptide with a large number of deleted C-terminal amino acid residues may retain some biological or immunogenic activities. In fact, peptides composed of as few as six amino acid residues may often evoke an immune response.

**[0124]** Accordingly, the present invention further provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the polypeptide shown in Figures 1A-G (SEQ ID NO:130), as described by the general formula 1-n, where n is an integer from 6 to 759, where n corresponds to the position of the amino acid residue identified in SEQ ID NO:130. More in particular, the invention provides polynucleotides encoding polypeptides comprising, or

alternatively consisting of, an amino acid sequence selected from the group: M-1 to A-759; M-1 to K-758; M-1 to K-757; M-1 to Q-756; M-1 to M-755; M-1 to L-754; M-1 to E-753; M-1 to L-752; M-1 to K-751; M-1 to R-750; M-1 to R-749; M-1 to L-748; M-1 to L-747; M-1 to G-746; M-1 to Y-745; M-1 to N-744; M-1 to E-743; M-1 to K-742; M-1 to T-741; M-1 to G-740; M-1 to S-739; M-1 to A-738; M-1 to T-737; M-1 to P-736; M-1 to D-735; M-1 to L-734; M-1 to Q-733; M-1 to L-732; M-1 to S-731; M-1 to I-730; M-1 to E-729; M-1 to Y-728; M-1 to H-727; M-1 to K-726; M-1 to K-725; M-1 to A-724; M-1 to L-723; M-1 to D-722; M-1 to L-721; M-1 to H-720; M-1 to G-719; M-1 to W-718; M-1 to R-717; M-1 to H-716; M-1 to Y-715; M-1 to L-714; M-1 to V-713; M-1 to A-712; M-1 to L-711; M-1 to N-710; M-1 to G-709; M-1 to H-708; M-1 to Y-707; M-1 to S-706; M-1 to A-705; M-1 to A-704; M-1 to N-703; M-1 to P-702; M-1 to N-701; M-1 to A-700; M-1 to K-699; M-1 to I-698; M-1 to A-697; M-1 to K-696; M-1 to L-695; M-1 to F-694; M-1 to L-693; M-1 to A-692; M-1 to E-691; M-1 to S-690; M-1 to E-689; M-1 to K-688; M-1 to Y-687; M-1 to K-686; M-1 to Q-685; M-1 to S-684; M-1 to K-683; M-1 to G-682; M-1 to L-681; M-1 to V-680; M-1 to N-679; M-1 to A-678; M-1 to L-677; M-1 to S-676; M-1 to F-675; M-1 to M-674; M-1 to L-673; M-1 to S-672; M-1 to H-671; M-1 to D-670; M-1 to N-669; M-1 to P-668; M-1 to I-667; M-1 to L-666; M-1 to E-665; M-1 to L-664; M-1 to A-663; M-1 to E-662; M-1 to R-661; M-1 to G-660; M-1 to V-659; M-1 to A-658; M-1 to E-657; M-1 to A-656; M-1 to Q-655; M-1 to A-654; M-1 to L-653; M-1 to N-652; M-1 to G-651; M-1 to T-650; M-1 to N-649; M-1 to D-648; M-1 to L-647; M-1 to L-646; M-1 to I-645; M-1 to I-644; M-1 to M-643; M-1 to N-642; M-1 to N-641; M-1 to W-640; M-1 to A-639; M-1 to L-638; M-1 to S-637; M-1 to H-636; M-1 to E-635; M-1 to P-634; M-1 to K-633; M-1 to L-632; M-1 to V-631; M-1 to T-630; M-1 to A-629; M-1 to N-628; M-1 to R-627; M-1 to W-626; M-1 to A-625; M-1 to N-624; M-1 to L-623; M-1 to A-622; M-1 to D-621; M-1 to V-620; M-1 to H-619; M-1 to R-618; M-1 to N-617; M-1 to L-616; M-1 to D-615; M-1 to A-614; M-1 to Y-613; M-1 to L-612; M-1 to R-611; M-1 to G-610; M-1 to L-609; M-1 to N-608; M-1 to Y-607; M-1 to Y-606; M-1 to C-605; M-1 to D-604; M-1 to P-603; M-1 to Y-602; M-1 to K-601; M-1 to R-600; M-1 to R-599; M-1 to H-598; M-1 to K-597; M-1 to I-596; M-1 to A-595; M-1 to T-594; M-1 to R-593; M-1 to Y-592; M-1 to S-591; M-1 to Q-590; M-1

to E-589; M-1 to A-588; M-1 to A-587; M-1 to E-586; M-1 to F-585; M-1 to R-584; M-1 to K-583; M-1 to L-582; M-1 to S-581; M-1 to N-580; M-1 to Q-579; M-1 to V-578; M-1 to I-577; M-1 to G-576; M-1 to L-575; M-1 to N-574; M-1 to M-573; M-1 to W-572; M-1 to A-571; M-1 to A-570; M-1 to A-569; M-1 to F-568; M-1 to D-567; M-1 to P-566; M-1 to Q-565; M-1 to I-564; M-1 to Q-563; M-1 to V-562; M-1 to A-561; M-1 to L-560; M-1 to S-559; M-1 to L-558; M-1 to L-557; M-1 to E-556; M-1 to E-555; M-1 to A-554; M-1 to E-553; M-1 to Q-552; M-1 to L-551; M-1 to E-550; M-1 to N-549; M-1 to R-548; M-1 to E-547; M-1 to K-546; M-1 to L-545; M-1 to I-544; M-1 to N-543; M-1 to G-542; M-1 to L-541; M-1 to N-540; M-1 to N-539; M-1 to M-538; M-1 to A-537; M-1 to H-536; M-1 to V-535; M-1 to Y-534; M-1 to K-533; M-1 to P-532; M-1 to N-531; M-1 to L-530; M-1 to R-529; M-1 to V-528; M-1 to A-527; M-1 to E-526; M-1 to R-525; M-1 to Y-524; M-1 to Y-523; M-1 to R-522; M-1 to I-521; M-1 to A-520; M-1 to A-519; M-1 to T-518; M-1 to Q-517; M-1 to N-516; M-1 to G-515; M-1 to K-514; M-1 to D-513; M-1 to A-512; M-1 to L-511; M-1 to N-510; M-1 to K-509; M-1 to G-508; M-1 to I-507; M-1 to N-506; M-1 to Y-505; M-1 to H-504; M-1 to V-503; M-1 to K-502; M-1 to A-501; M-1 to N-500; M-1 to L-499; M-1 to P-498; M-1 to C-497; M-1 to V-496; M-1 to S-495; M-1 to L-494; M-1 to A-493; M-1 to S-492; M-1 to R-491; M-1 to F-490; M-1 to L-489; M-1 to Q-488; M-1 to E-487; M-1 to E-486; M-1 to S-485; M-1 to R-484; M-1 to W-483; M-1 to E-482; M-1 to G-481; M-1 to S-480; M-1 to R-479; M-1 to L-478; M-1 to V-477; M-1 to C-476; M-1 to R-475; M-1 to L-474; M-1 to T-473; M-1 to N-472; M-1 to I-471; M-1 to F-470; M-1 to L-469; M-1 to I-468; M-1 to G-467; M-1 to L-466; M-1 to V-465; M-1 to V-464; M-1 to A-463; M-1 to A-462; M-1 to I-461; M-1 to L-460; M-1 to K-459; M-1 to K-458; M-1 to K-457; M-1 to K-456; M-1 to T-455; M-1 to H-454; M-1 to K-453; M-1 to S-452; M-1 to L-451; M-1 to A-450; M-1 to G-449; M-1 to F-448; M-1 to G-447; M-1 to F-446; M-1 to T-445; M-1 to L-444; M-1 to L-443; M-1 to V-442; M-1 to C-441; M-1 to Y-440; M-1 to G-439; M-1 to X-438; M-1 to S-437; M-1 to P-436; M-1 to L-435; M-1 to Y-434; M-1 to L-433; M-1 to V-432; M-1 to R-431; M-1 to E-430; M-1 to A-429; M-1 to V-428; M-1 to V-427; M-1 to F-426; M-1 to G-425; M-1 to V-424; M-1 to R-423; M-1 to F-422; M-1 to F-421; M-1 to L-420; M-1 to N-419; M-1 to S-418; M-1 to A-417; M-1 to P-416; M-1 to L-415; M-1 to F-414; M-1

to P-413; M-1 to I-412; M-1 to V-411; M-1 to L-410; M-1 to F-409; M-1 to G-408; M-1 to L-407; M-1 to G-406; M-1 to L-405; M-1 to T-404; M-1 to L-403; M-1 to I-402; M-1 to R-401; M-1 to R-400; M-1 to K-399; M-1 to H-398; M-1 to G-397; M-1 to D-396; M-1 to E-395; M-1 to S-394; M-1 to C-393; M-1 to L-392; M-1 to A-391; M-1 to Q-390; M-1 to C-389; M-1 to I-388; M-1 to L-387; M-1 to G-386; M-1 to I-385; M-1 to L-384; M-1 to C-383; M-1 to F-382; M-1 to W-381; M-1 to L-380; M-1 to A-379; M-1 to A-378; M-1 to L-377; M-1 to A-376; M-1 to I-375; M-1 to V-374; M-1 to R-373; M-1 to W-372; M-1 to D-371; M-1 to S-370; M-1 to I-369; M-1 to S-368; M-1 to K-367; M-1 to I-366; M-1 to L-365; M-1 to P-364; M-1 to I-363; M-1 to C-362; M-1 to G-361; M-1 to M-360; M-1 to S-359; M-1 to W-358; M-1 to D-357; M-1 to F-356; M-1 to C-355; M-1 to L-354; M-1 to W-353; M-1 to W-352; M-1 to P-351; M-1 to C-350; M-1 to L-349; M-1 to L-348; M-1 to L-347; M-1 to W-346; M-1 to A-345; M-1 to N-344; M-1 to L-343; M-1 to S-342; M-1 to Y-341; M-1 to Y-340; M-1 to Y-339; M-1 to N-338; M-1 to Y-337; M-1 to N-336; M-1 to V-335; M-1 to A-334; M-1 to R-333; M-1 to V-332; M-1 to L-331; M-1 to M-330; M-1 to S-329; M-1 to D-328; M-1 to A-327; M-1 to F-326; M-1 to S-325; M-1 to A-324; M-1 to P-323; M-1 to N-322; M-1 to D-321; M-1 to V-320; M-1 to E-319; M-1 to T-318; M-1 to F-317; M-1 to A-316; M-1 to X-315; M-1 to P-314; M-1 to G-313; M-1 to T-312; M-1 to G-311; M-1 to M-310; M-1 to I-309; M-1 to R-308; M-1 to W-307; M-1 to R-306; M-1 to V-305; M-1 to Y-304; M-1 to L-303; M-1 to M-302; M-1 to G-301; M-1 to A-300; M-1 to G-299; M-1 to G-298; M-1 to S-297; M-1 to T-296; M-1 to L-295; M-1 to L-294; M-1 to T-293; M-1 to M-292; M-1 to R-291; M-1 to F-290; M-1 to L-289; M-1 to L-288; M-1 to G-287; M-1 to G-286; M-1 to N-285; M-1 to R-284; M-1 to L-283; M-1 to M-282; M-1 to G-281; M-1 to L-280; M-1 to N-279; M-1 to E-278; M-1 to L-277; M-1 to S-276; M-1 to K-275; M-1 to D-274; M-1 to K-273; M-1 to H-272; M-1 to L-271; M-1 to V-270; M-1 to K-269; M-1 to Q-268; M-1 to X-267; M-1 to I-266; M-1 to E-265; M-1 to L-264; M-1 to V-263; M-1 to N-262; M-1 to F-261; M-1 to K-260; M-1 to G-259; M-1 to I-258; M-1 to V-257; M-1 to L-256; M-1 to I-255; M-1 to D-254; M-1 to F-253; M-1 to V-252; M-1 to A-251; M-1 to N-250; M-1 to L-249; M-1 to G-248; M-1 to L-247; M-1 to V-246; M-1 to T-245; M-1 to I-244; M-1 to G-243; M-1 to Q-242; M-1 to E-241; M-1 to K-240; M-1 to C-239; M-1 to L-238;

M-1 to M-237; M-1 to A-236; M-1 to V-235; M-1 to A-234; M-1 to G-233; M-1 to L-232; M-1 to F-231; M-1 to I-230; M-1 to S-229; M-1 to L-228; M-1 to L-227; M-1 to V-226; M-1 to W-225; M-1 to F-224; M-1 to T-223; M-1 to S-222; M-1 to S-221; M-1 to H-220; M-1 to A-219; M-1 to G-218; M-1 to E-217; M-1 to K-216; M-1 to N-215; M-1 to S-214; M-1 to E-213; M-1 to R-212; M-1 to F-211; M-1 to A-210; M-1 to K-209; M-1 to C-208; M-1 to Y-207; M-1 to G-206; M-1 to L-205; M-1 to F-204; M-1 to S-203; M-1 to L-202; M-1 to L-201; M-1 to F-200; M-1 to F-199; M-1 to L-198; M-1 to A-197; M-1 to C-196; M-1 to L-195; M-1 to L-194; M-1 to D-193; M-1 to A-192; M-1 to R-191; M-1 to G-190; M-1 to V-189; M-1 to V-188; M-1 to G-187; M-1 to A-186; M-1 to V-185; M-1 to C-184; M-1 to E-183; M-1 to T-182; M-1 to H-181; M-1 to V-180; M-1 to P-179; M-1 to H-178; M-1 to V-177; M-1 to A-176; M-1 to F-175; M-1 to L-174; M-1 to L-173; M-1 to A-172; M-1 to A-171; M-1 to L-170; M-1 to L-169; M-1 to S-168; M-1 to A-167; M-1 to R-166; M-1 to P-165; M-1 to A-164; M-1 to L-163; M-1 to H-162; M-1 to L-161; M-1 to R-160; M-1 to R-159; M-1 to G-158; M-1 to K-157; M-1 to S-156; M-1 to T-155; M-1 to Y-154; M-1 to Q-153; M-1 to L-152; M-1 to G-151; M-1 to G-150; M-1 to F-149; M-1 to L-148; M-1 to V-147; M-1 to S-146; M-1 to F-145; M-1 to V-144; M-1 to D-143; M-1 to V-142; M-1 to M-141; M-1 to L-140; M-1 to V-139; M-1 to S-138; M-1 to I-137; M-1 to G-136; M-1 to S-135; M-1 to H-134; M-1 to L-133; M-1 to L-132; M-1 to I-131; M-1 to N-130; M-1 to V-129; M-1 to V-128; M-1 to H-127; M-1 to F-126; M-1 to G-125; M-1 to V-124; M-1 to P-123; M-1 to H-122; M-1 to F-121; M-1 to G-120; M-1 to G-119; M-1 to S-118; M-1 to L-117; M-1 to Y-116; M-1 to Y-115; M-1 to N-114; M-1 to I-113; M-1 to R-112; M-1 to F-111; M-1 to T-110; M-1 to L-109; M-1 to V-108; M-1 to T-107; M-1 to L-106; M-1 to P-105; M-1 to R-104; M-1 to Y-103; M-1 to S-102; M-1 to K-101; M-1 to H-100; M-1 to S-99; M-1 to T-98; M-1 to N-97; M-1 to S-96; M-1 to S-95; M-1 to L-94; M-1 to R-93; M-1 to S-92; M-1 to G-91; M-1 to W-90; M-1 to F-89; M-1 to D-88; M-1 to H-87; M-1 to H-86; M-1 to W-85; M-1 to L-84; M-1 to D-83; M-1 to G-82; M-1 to L-81; M-1 to P-80; M-1 to T-79; M-1 to E-78; M-1 to A-77; M-1 to Q-76; M-1 to L-75; M-1 to D-74; M-1 to K-73; M-1 to N-72; M-1 to N-71; M-1 to V-70; M-1 to I-69; M-1 to A-68; M-1 to E-67; M-1 to S-66; M-1 to D-65; M-1 to D-64; M-1 to F-63; M-1 to V-62; M-1 to F-61; M-1 to D-60; M-1 to G-59; M-

1 to D-58; M-1 to Y-57; M-1 to S-56; M-1 to R-55; M-1 to A-54; M-1 to F-53; M-1 to C-52; M-1 to V-51; M-1 to I-50; M-1 to A-49; M-1 to V-48; M-1 to S-47; M-1 to G-46; M-1 to V-45; M-1 to V-44; M-1 to L-43; M-1 to K-42; M-1 to A-41; M-1 to W-40; M-1 to F-39; M-1 to P-38; M-1 to P-37; M-1 to L-36; M-1 to V-35; M-1 to S-34; M-1 to S-33; M-1 to P-32; M-1 to L-31; M-1 to I-30; M-1 to H-29; M-1 to D-28; M-1 to L-27; M-1 to D-26; M-1 to T-25; M-1 to D-24; M-1 to L-23; M-1 to V-22; M-1 to A-21; M-1 to M-20; M-1 to R-19; M-1 to F-18; M-1 to V-17; M-1 to A-16; M-1 to P-15; M-1 to Q-14; M-1 to H-13; M-1 to S-12; M-1 to G-11; M-1 to A-10; M-1 to G-9; M-1 to A-8; M-1 to N-7; and M-1 to H-6 of SEQ ID NO: 130. Polypeptides encoded by these polynucleotides are also encompassed by the invention.

**[0125]** In addition, any of the above listed N- or C-terminal deletions can be combined to produce a N- and C-terminal deleted polypeptide. The invention also provides polypeptides comprising, or alternatively consisting of, one or more amino acids deleted from both the amino and the carboxyl termini, which may be described generally as having residues m-n of SEQ ID NO:130, where n and m are integers as described above. Polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0126]** The present invention is also directed to proteins containing polypeptides at least 80%, 85%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to a polypeptide sequence set forth herein as m-n. In preferred embodiments, the application is directed to proteins containing polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to polypeptides having the amino acid sequence of the specific N- and C-terminal deletions recited herein. Polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0127]** Also included are polynucleotide sequences encoding a polypeptide consisting of a portion of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit No. 209745, where this portion excludes any integer of amino acid residues from 1 to about 755 amino acids from the amino terminus of the complete amino acid sequence encoded by a cDNA clone contained in ATCC Deposit No. 209745, or any integer of amino acid residues from 6 to about 759 amino acids from the carboxy terminus, or any combination of the above amino terminal and



carboxy terminal deletions, of the complete amino acid sequence encoded by the cDNA clone contained in ATCC Deposit No. 209745. Polypeptides encoded by these polynucleotides also are encompassed by the invention.

**[0128]** As described herein or otherwise known in the art, the polynucleotides of the invention have uses that include, but are not limited to, serving as probes or primers in chromosome identification, chromosome mapping, and linkage analysis.

**[0129]** This gene is expressed primarily in ovarian cancer tissues and substantia nigra and, to a lesser extent, in amygdala and brain, striatum.

**[0130]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative disorders and/or disorders of the reproductive system, including, but not limited to ovarian cancer. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system and brain and/or reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., CNS, neural, nervous, neuronal, reproductive, ovarian, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, vaginal pool, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one, two or all three of the immunogenic epitopes shown in SEQ ID NO: 130 as residues: Arg-93 to Arg-104, Tyr-154 to Arg-159, Arg-212 to His-220. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0131]** The tissue distribution in substantia nigra and, to a lesser extent, in amygdala and brain, striatum, indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of

neurodegenerative disease states, behavioral disorders; or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival.

**[0132]** The tissue distribution in reproductive and developing tissues indicates that polynucleotides and/or polypeptides corresponding to this gene would be useful for the treatment, prevention, detection, and/or diagnosis of disorders of reproductive system organs, including cancers, disorders affecting fertility, and/or developmental disorders. Specifically, expression in ovarian cancer tissue, indicates that polynucleotides and/or polypeptides corresponding to this gene, agonists, and/or antagonists thereof (including, but not limited to antibodies or fragments thereof, that bind polypeptides of the invention) would be useful for the treatment, prevention, detection and diagnosis of conditions concerning proper ovarian function (e.g., egg maturation, endocrine function), as well as cancer. The expression in ovarian tissue may indicate that polynucleotides and/or polypeptides corresponding to this gene, agonists, and/or antagonists thereof (including, but not limited to antibodies or fragments thereof, that bind polypeptides of the invention) can be used to treat, prevent, detect and/or diagnose disorders of the ovary, including inflammatory disorders, such as oophoritis (e.g., caused by viral or bacterial infection), ovarian cysts, amenorrhea, infertility, hirsutism, and ovarian cancer (including, but not limited to, primary and secondary cancerous growth, endometrioid carcinoma of the ovary,

ovarian papillary serous adenocarcinoma, ovarian mucinous adenocarcinoma, Ovarian Krukenberg tumor).

**[0133]** Moreover, the predicted membrane localization indicates that polynucleotides and/or polypeptides corresponding to this gene would be a good target for antagonists, particularly small molecules or antibodies, which block functional activity (such as, for example, binding of the receptor by its cognate ligand(s); transport function; signalling function). Accordingly, preferred are antibodies and or small molecules which specifically bind an extracellular portion of the translation product of this gene. The extracellular regions can be ascertained from the information regarding the transmembrane domains as set out above. Also provided is a kit for detecting cancer. In one embodiment, the kit would be useful for detecting ovarian cancer. Such a kit comprises in one embodiment an antibody specific for the translation product of this gene bound to a solid support. Also provided is a method of detecting cancer (for example, ovarian cancer) in an individual which comprises a step of contacting an antibody specific for the translation product of this gene to a bodily fluid from the individual, preferably serum, and ascertaining whether antibody binds to an antigen found in the bodily fluid. Preferably the antibody is bound to a solid support and the bodily fluid is serum. The above embodiments, as well as other treatments and diagnostic tests (kits and methods), are more particularly described elsewhere herein. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0134]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:23 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the

general formula of a-b, where a is any integer between 1 to 3872 of SEQ ID NO:23, b is an integer of 15 to 3886, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:23, and where b is greater than or equal to a + 14.

**[0135] FEATURES OF PROTEIN ENCODED BY GENE NO: 14**

**[0136]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group: RDNDYLLHGHRRPPMF (SEQ ID NO:290), SFRACFKSIFRIHTETGNIWTHLL (SEQ ID NO:291), and/or GFVLFLFLGILTMLRPNMYFMAPLQEKVV (SEQ ID NO:292). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0137]** The gene encoding the disclosed cDNA is thought to reside on chromosome 1. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 1.

**[0138]** This gene is expressed primarily in bone marrow, fetal liver and spleen tissues, several types of leukocytes including neutrophils, and T-cells, placental tissue, and brain tissue.

**[0139]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders of the immune system and central nervous system including AIDS, Lupus, hemotological cancers, mood disorders, and dementia. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the

immune system and central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one, two or all three of the immunogenic epitopes shown in SEQ ID NO: 131 as residues: Glu-24 to Tyr-35, Arg-83 to Thr-92, Pro-148 to Gly-154. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

[0140] The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of a variety of immune system disorders. Representative uses are described in the 'Immune Activity' and 'Infectious Disease' sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product in fetal liver and spleen tissues, and several types of leukocytes, indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. Polynucleotides and polypeptides of the invention may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, polynucleotides and polypeptides of the invention, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, polynucleotides and polypeptides of the invention may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell

types. Alternatively, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, diagnosis, prevention and/or treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0141]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:24 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1569 of SEQ ID NO:24, b is an integer of 15 to 1583, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:24, and where b is greater than or equal to a + 14.

**[0142] FEATURES OF PROTEIN ENCODED BY GENE NO: 15**

**[0143]** The translation product of this gene shares sequence homology with gp25L, which is thought to be important in protein processing.

**[0144]** This gene is expressed primarily in stimulated synovium, cerebellum, immune cells (e.g., T-cells), and placental tissues, and, to a lesser extent, in several other tissues and organs.

**[0145]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, inflammation, disorders of developing systems, central nervous system, and musculo-skeletal system. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, central nervous system, musculo-skeletal, and developing systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, neural, musculo-skeletal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0146]** The tissue distribution and homology to gp25L indicates that polynucleotides and polypeptides corresponding to this gene would be useful for treatment, prevention, detection and/or diagnosis of disorders of immune, central nervous system, musculo-skeletal, and developing systems. In addition, the expression of this gene product in synovium indicates a role in the detection and treatment of disorders and conditions affecting the skeletal system, in particular osteoporosis as well as disorders afflicting connective tissues (e.g., arthritis, trauma, tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e., spondyloepiphyseal dysplasia congenita, familial arthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). The tissue distribution and homology to gp25L indicates that the

polynucleotides and polypeptides of the invention would be useful for treatment, prevention, detection and/or diagnosis of disorders associated with expression of Gp25L-H, e.g. Cushing's disease, cystic fibrosis, diabetes mellitus, diabetes insipidus, glucose-galactose malabsorption syndrome, hypercholesterolemia, hyper and hypoglycemia, Grave's disease, goiter, inflammation and autoimmune disorders including Addison's disease, adult respiratory distress syndrome, allergies (including hay fever and hives), anemia, asthma, atherosclerosis, bronchitis, cholecystitis, Crohn's disease, ulcerative colitis, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, atrophic gastritis, glomerulonephritis, gout, hypereosinophilia, irritable bowel syndrome, lupus erythematosus, multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, osteoarthritis, osteoporosis, pancreatitis, polymyositis, rheumatoid arthritis, scleroderma, Sjogren's syndrome and autoimmune thyroiditis, complications of cancer, hemodialysis, extracorporeal circulation; viral, bacterial, fungal, parasitic, protozoal and helminthic infections and trauma. The tissue distribution in T-cells indicates that polynucleotides and polypeptides of the invention would be useful for the diagnosis, detection, prevention and/or treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. Involvement in the regulation of cytokine production, antigen presentation, or other processes indicates a usefulness for treatment of cancer (e.g. by boosting immune responses). Expression in cells of lymphoid origin, indicates the natural gene product would be involved in immune functions. Therefore it would also be useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus



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erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0147]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:25 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1655 of SEQ ID NO:25, b is an integer of 15 to 1669, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:25, and where b is greater than or equal to a + 14.

**[0148] FEATURES OF PROTEIN ENCODED BY GENE NO: 16**

**[0149]** The translation product of this gene shares sequence homology with ribosomal proteins (see, e.g., Genbank accession number gi|437926 and PID|d1011606; all references available through these accessions are hereby incorporated in their entirety by reference herein). Based on the sequence similarity, the translation product of this clone is expected to share at least some biological activities with ribosomal proteins.

**[0150]** This gene is expressed primarily in immune and hematopoietic cells, fetal tissue, adipose tissue, uterine cancer tissue, ovary tumor, breast and brain tissues, and, to a lesser extent, in several other tissues.

**[0151]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and hematopoietic disorders, disorders of the central nervous system and reproductive organs. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, hematopoietic, central nervous system and reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, reproductive, neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0152]** The tissue distribution in breast, brain, and immune tissues indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the treatment, prevention, detection and/or diagnosis of disorders of the immune, hematopoietic, central nervous and reproductive systems. Moreover, the expression within fetal tissues and other cellular sources marked by proliferating cells indicates that polynucleotides and polypeptides of the invention may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers,

or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain degenerative disorders, such as spinal muscular atrophy (SMA). Alternatively, this gene product may be involved in the pattern of cellular proliferation that accompanies early embryogenesis. Thus, aberrant expression of this gene product in tissues - particularly adult tissues - may correlate with patterns of abnormal cellular proliferation, such as found in various cancers. Because of potential roles in proliferation and differentiation, polynucleotides and polypeptides of the invention may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention would be useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein would be useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0153]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:26 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1039 of SEQ ID NO:26, b is an integer of 15 to 1053, where both a and b correspond to the positions of

nucleotide residues shown in SEQ ID NO:26, and where b is greater than or equal to a + 14.

**[0154] FEATURES OF PROTEIN ENCODED BY GENE NO: 17**

**[0155]** The gene encoding the disclosed cDNA is believed to reside on chromosome 11. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 11.

**[0156]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group:

TGPEFPGSNSTVARRIKDLAADIEEELVCRLKICDGFSLQLDESADVSGLAVLL  
VFVRYRFNKSIEEDLLLCESLQSNATGEEIFNCINSFMQKHEIEWEKCVDVCSD  
ASRAVDGKIAEAVTLIKYVAPESTSSHCLLYRHALAVKIMPTSLKNVLDQAV  
QIINYIKARPHQSRLKILCEEMGAQHTALLNTEVRWLSRGKVLVRLFELRR  
ELLVFMDSAFRLSDCLTNSSWLLRLAYLADIFTKLNEVNLSMQGKNVTVFTV  
FDKMSSLLRKLEFWASSVEEENFDCFPTLSDFLTEINSTVDKDICS AIVQHRLG  
LRATLLKYFPVTNDNNAWVRNPFTVTVPKASLVARDYESLIDLTSDSQVKQN  
FSELSLNDFWSSLIQEYPSIARRAVRVLLPFATMHL CETGFSYYAATKTKYRK  
RLDAAPHMRIRLSNITPNIKRICDKKTQKHCSH (SEQ ID NO:293),  
DIEEELVCRLKICDGFSLQLDESADVSGLAV (SEQ ID NO:294),  
NSFMQKHEIEWEKCVDVCSDASRAVDGKIAEAVTLI (SEQ ID NO:295),  
LDQAVQIINYIKARPHQSRLKILCEEMGAQHTALL (SEQ ID NO:296),  
SAFRLSDCLTNSSWLLRLAYLADIFTKLNEVNLSMQGKNVTVFTVFDKM  
(SEQ ID NO:297), SDFLTEINSTVDKDICS AIVQHRLGLRATLLK (SEQ ID  
NO:298), and/or SDSQVKQNFSELSLNDFWSSLIQEYPSIARRAVRVLLP (SEQ  
ID NO:299). Moreover, fragments and variants of these polypeptides (such as, for  
example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%,  
96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides  
encoded by a polynucleotide which hybridizes, under stringent conditions, to the  
polynucleotide encoding these polypeptides) are encompassed by the invention.  
Antibodies that bind polypeptides of the invention and polynucleotides encoding  
these polypeptides are also encompassed by the invention.

**[0157]** This gene is expressed primarily in spleen from a chronic lymphocytic leukemia patient, and hodgkin's lymphoma, and, to a lesser extent, in pancreatic islet cell tumors and activated T cells.

**[0158]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, chronic lymphocytic leukemia; hodgkin's lymphoma; pancreatic islet cell cancer; cancer in general; hematopoietic disorders; immune dysfunction. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and pancreas, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hematopoietic, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0159]** The tissue distribution in spleen from a chronic lymphocytic leukemia patient, and hodgkin's lymphoma, pancreatic islet cell tumors, and activated T-cells indicates that polynucleotides and/or polypeptides corresponding to this gene would be useful in the treatment, prevention, detection and/or diagnosis of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the protein product of this gene would be useful for the diagnosis and/or treatment of a variety of cancers, including CLL; Hodgkin's lymphoma; and pancreatic cancer. Expression of this gene product in a variety of cancers indicates that it may be a bad player and may likely be a target for inhibitors as therapeutics. Alternately, this gene product may be expressed in both normal and abnormal hematopoietic tissues, where it may play necessary roles in the proliferation; survival; differentiation; or activation of hematopoietic cell lineages. Likewise, expression in

pancreatic islet cell tumors may simply reflect a necessary role that this protein plays in normal pancreatic function. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0160]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:27 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1463 of SEQ ID NO:27, b is an integer of 15 to 1477, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:27, and where b is greater than or equal to a + 14.

**[0161] FEATURES OF PROTEIN ENCODED BY GENE NO: 18**

**[0162]** When tested against U937 Myeloid cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that this gene activates myeloid cells, and to a lesser extent other cells, through the Jak-STAT signal transduction pathway. The gamma activating sequence (GAS) is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

**[0163]** The polypeptide of this gene has been determined to have transmembrane domains at about amino acid positions 219 to about 235, at about 114 to about 130, at

about 86 to about 102, and at about 43 to about 59 of the amino acid sequence referenced in Table 1 for this gene. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type IIIa membrane proteins.

**[0164]** The gene encoding the disclosed cDNA is believed to reside on chromosome 17. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 17.

**[0165]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

DPRVRECLQDWASFLRLAIPSMMLCMEWWAYEVGSFLSGILGMVELGAQS  
IVYELAIIVYMVPAGFSVAASVRVGNALGAGDMEQARKSSTVSLITVLF  
AFSVLLLSCKDHVGYIFTTDRDIINLVAQVVPIYAVSHLFEALACTSGGVLRGS  
GNQKVGAIVNTIGXYVVGLPIGIALMFATTLGVMGLWSGIICTVFQAVCFLG  
FIIQLNWKKACXQAQVHANLKVNNVPRSGNSALPQDPLHPGCPENLEGILTN  
DVGKTGEPQSDQQMRQEEPLPEHPQDGAKLSRKQLVLRRLGLLLGVFLILLV  
GILVRFYVRIQ (SEQ ID NO:300). Moreover, fragments and variants of these

polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0166]** This gene is expressed primarily in endometrial tumor tissue, cartilage tissue, fetal tissue, immune tissue (B-cells and macrophages), and to a lesser extent in several other tissues and organs.

**[0167]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, tumors and disorders of the musculo-skeletal system. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell

type(s). For a number of disorders of the above tissues or cells, particularly of the musculo-skeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., musculo-skeletal, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of the immunogenic epitopes shown in SEQ ID NO: 135 as residues: Met-1 to Ser-8. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

[0168] The tissue distribution in musculo-skeletal tissues and biological activity in the GAS assay, indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the treatment, prevention, detection and/or diagnosis of disorders of the musculo-skeletal system, and cancers thereof. The tissue distribution in immune cells (e.g., B-cells and macrophages) and biological activity in the GAS assay indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. Involvement in the regulation of cytokine production, antigen presentation, or other processes indicates a usefulness for treatment of cancer (e.g., by boosting immune responses). Expression in cells of lymphoid origin, indicates the natural gene product would be involved in immune functions. Therefore it would also be useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to



transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. In addition, the expression of this gene product in cartilage tissue indicates a role in the detection and treatment of disorders and conditions affecting the skeletal system, in particular osteoporosis as well as disorders afflicting connective tissues (e.g., arthritis, trauma, tendonitis, chondromalacia and inflammation), such as in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e., spondyloepiphyseal dysplasia congenita, familial arthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0169]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:28 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2490 of SEQ ID NO:28, b is an integer of 15 to 2504, where both a and b correspond to the positions of

nucleotide residues shown in SEQ ID NO:28, and where b is greater than or equal to a + 14.

**[0170] FEATURES OF PROTEIN ENCODED BY GENE NO: 19**

**[0171]** The gene encoding the disclosed cDNA is thought to reside on chromosome 17. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 17.

**[0172]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

GTRIHTILVYQESNRKMDSVDPASSQAMELSDVTLIEGVGNEVMVVAGVVVL  
ILALVLAWLSTYVADSGSNQLLGAIVSAGDTSVLHLGHVDHLVAGQGNPEPT  
ELPHPSEGNDKAEAEAGEGRGDSTGEAGAGGGVEPSLEHLLDIQGLPKRQAG  
AGSSSPEAPLRSEDSTCLPPSPGLITVRLKFLNDTEELAVARPEDTVGALKSKY  
FPGQESQMCLIYQGRLLQDPARTLRSLNITDNCVIHCHRSPPGSAVPGPSASLA  
PSATEPPSLGVNVGSLMVPVFVLLGVVWYFRINYRQFFTAPATVSLVGVTV  
FFSFLVFGMYGR (SEQ ID NO: 301). Moreover, fragments and variants of these

polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0173]** The polypeptide of this gene has been determined to have transmembrane domains at about amino acid positions 234 to about 250 and at about 266 to about 282 of the amino acid sequence referenced in Table 1 for this gene. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type IIIa membrane proteins.

**[0174]** This gene is expressed primarily in breast and cerebellum tissues, ovary cancer tissue, B-cells, tonsils, as well as in cells of the hematopoietic system, and, to a lesser extent, in several other organs and tissues.

**[0175]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders of the brain, reproductive system and hematopoietic system. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hematopoietic system, central nervous system and reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, neural, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one, two, three or all four of the immunogenic epitopes shown in SEQ ID NO: 136 as residues: Gly-56 to Gly-86, Leu-107 to Ala-112, Ala-121 to Thr-129, Lys-164 to Gln-174. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0176]** The tissue distribution in immune, reproductive, and neural tissues indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the treatment, prevention, detection and/or diagnosis of disorders of the immune and haemopoietic system, the central nervous system, and the reproductive system. Furthermore, the expression in the breast tissue may indicate its uses in breast neoplasia and breast cancers, such as fibroadenoma, papillary carcinoma, ductal carcinoma, Paget's disease, medullary carcinoma, mucinous carcinoma, tubular carcinoma, secretory carcinoma and apocrine carcinoma, as well as juvenile hypertrophy and gynecomastia, mastitis and abscess, duct ectasia, fat necrosis and fibrocystic diseases. Alternatively, the tissue distribution in cerebellum tissue indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, prevention and/or diagnosis of neurodegenerative

disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. In addition, the tissue distribution in immune system cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, diagnosis, prevention and/or treatment of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. This gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0177]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:29 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the

general formula of a-b, where a is any integer between 1 to 1852 of SEQ ID NO:29, b is an integer of 15 to 1866, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:29, and where b is greater than or equal to a + 14.

**[0178] FEATURES OF PROTEIN ENCODED BY GENE NO: 20**

**[0179]** The translation product of this gene shares weak sequence homology with dehydrogenase enzymes (see, e.g., gnl|PID|e1316908, all references available through this accession are hereby incorporated in their entirety by reference herein) which are thought to be important in a variety of enzymatic conversions, including the biosynthesis of clavulanic acid from a precursor clavulanic acid aldehyde. The obtained clavulanic acid is in turn a key ingredient in antibiotics.

**[0180]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group: DSRISLLVNNAGVGATASLLESDADK (SEQ ID NO:302) and/or MDAMILLNVLALTRLAKAAATNFVAQGRGTIINIGSIVALAPKVLNGVYGGT KAFVQAFSESLQHELSDKGVVVQVVLPGATATEFWDIAGLPVNNLPEAMVM TTENLVXAALAGLAQGEAVTIPSLPDSADWDTYERARLALGPNLSHREPAAR YGLK (SEQ ID NO:303). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0181]** This gene is expressed primarily in CD34 positive hematopoietic cells.

**[0182]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic diseases and/or disorders; impaired immune function; lymphomas and leukemias. Similarly, polypeptides and antibodies directed to these

polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hematopoietic, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of, the immunogenic epitopes shown in SEQ ID NO: 137 as residues: Pro-97 to Pro-113. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

[0183] The tissue distribution in CD34 positive hematopoietic cells indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis, detection, prevention and/or treatment of a variety of hematopoietic disorders. Expression of this gene product specifically in CD34 positive cells indicates that it plays a role in early events of hematopoiesis, including proliferation; survival; differentiation; and activation of early stem and committed progenitor cells. Polynucleotides and polypeptides corresponding to this gene would be useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of

various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0184]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:30 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1487 of SEQ ID NO:30, b is an integer of 15 to 1501, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:30, and where b is greater than or equal to a + 14.

**[0185] FEATURES OF PROTEIN ENCODED BY GENE NO: 21**

**[0186]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group:  
GTPAGTGPEFPGRPTRPSRTESAQTTQHSPLRPLWRLKRDSSPCHPQTRADWG  
VCPWGGAAQGLRPGCHLAPRRCLCPGSCCPWHWAEAQWSFLWRGLWGLR  
TLPTALRASPAASGTVTYSACLGTSCLLRAPCWRLRT CRQSWC (SEQ ID  
NO:304), GTPAGTGPEFPGRPTRPSRTESAQTTQH (SEQ ID NO:305),  
SPLRPLWRLKRDSSPCHPQTRADWGVCPW (SEQ ID NO:306),  
GGAAQGLRPGCHLAPRRCLCPGSCCPWHWA (SEQ ID NO:307),  
EAQWSFLWRGLWGLRTLPTALRASPAASGT (SEQ ID NO:308),  
VTYSACLGTSCLLRAPCWRLRTCRQSWC (SEQ ID NO:309), and/or  
MPVPWFLLSLALGRSPVVLSELRVVGPDATHCSPGLSCRLWDSILCLPGDI  
VPAPGPVLAPTHLQTELVLRCQKETDCDLCLRVAVHLAVHGHWEPEDEEK  
FGGAADLGVEEPRNASLQAQVVLSFQAYPTARCVLLEVQVPAALVQFGQSV

GSVVYDCFEAALGSEVRIWSYTQPRYEKELNHTQQLPDCRGLEWNSIPSCW  
 ALPWLNV SADGDNVHLVLNVSEEQHFGLSLYWNQVQGPPKPRWHKNLTGP  
 QIITLNHTDLVPCLCIQVWPLEPDSVRTNICPFREDPRAHQNLWQAARLRLLT  
 LQSWLLDAPCSLPAAALCWRAPGGDPCQPLVPPLSWENVTVDKVLEFPLLK  
 GHPNLCVQVNSSEKLQLQECLWADSLGPLKDDVLLLETRGPQDNRS LCALEP  
 SGCTSLPSKASTRAARLGEYLLQDLQSGQCLQLWDDDLGALWACPM D KYIH  
 KRWALVWLACLLFRRALSLILLKKDHAKGWLRLLLKQDVRS G (SEQ ID

NO:310). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0187]** The gene encoding the disclosed cDNA is believed to reside on chromosome 3. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 3.

**[0188]** This gene is expressed primarily in osteoarthritis, breast cancer, and uterine cancer, and, to a lesser extent, in brain.

**[0189]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer, particularly breast and uterine cancer; and neurological diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the breast, lymph node, and CNS, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, breast, skeletal, joint, neural, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, amniotic fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having



such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of the immunogenic epitopes shown in SEQ ID NO: 138 as residues: Gln-75 to Cys-80. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

[0190] The tissue distribution in breast and uterine cancer indicates that polynucleotides and/or polypeptides corresponding to this gene would be useful for the diagnosis, detection, prevention and/or treatment of a variety of cancers, particularly breast cancer and uterine cancer. Expression of this gene in brain also indicates that it may play a role in neurological function, and that its absence may lead to disorders such as Alzheimer's and/or Parkinson's disease. Expression of this gene product at elevated levels within cancerous tissue indicates that it may be a player in the progression of the disease, perhaps by driving proliferation or blocking differentiation or apoptosis. Therefore, beneficial therapeutics may be developed based upon attempts to block this gene product. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, polynucleotides and/or polypeptides corresponding to this gene may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention would be useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein would be useful in

modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[0191] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:31 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1738 of SEQ ID NO:31, b is an integer of 15 to 1752, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:31, and where b is greater than or equal to a + 14.

#### **[0192] FEATURES OF PROTEIN ENCODED BY GENE NO: 22**

[0193] This gene shares sequence homology with a yeast hypothetical 52.9 KD protein CDC26-YMR31 intergenic region (see, e.g. Genbank Accession No. gp|D50617|YSCCHRVI\_114; all references available through this accession are hereby incorporated in their entirety by reference herein).

[0194] This gene has been mapped to chromosome 18q22-23, and therefore can be used in linkage analysis as a marker for 18q22-23.

[0195] This gene is expressed primarily in whole brain tissue, as well as brain specific tissues such as hypothalamus, frontal cortex, cerebellum, amygdala, and hippocampus tissues, as well as other brain specific tissues.

**[0196]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, schizophrenia, developmental disorders, and abnormal mental states. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, brain, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one, two, three, four, five, six, seven, eight, nine or all ten of the immunogenic epitopes shown in SEQ ID NO: 139 as residues: Met-98 to Gln-107, Gly-120 to Gly-126, Pro-138 to Trp-145, Leu-159 to Gly-169, Val-211 to Arg-217, Cys-256 to His-262, Glu-320 to Val-327, Phe-399 to Asn-406, Asp-444 to Ser-450, Asp-475 to Trp-488. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0197]** The tissue distribution in whole brain tissue and brain specific tissues indicates that polynucleotides and polypeptides corresponding to this gene would be useful for treating, preventing, detecting and/or diagnosing neural and neurodegenerative disorders. Furthermore, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, diagnosis, prevention and/or treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the

treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Elevated expression of this gene product within the frontal cortex of the brain indicates that it may be involved in neuronal survival; synapse formation; conductance; neural differentiation, etc. Such involvement may impact many processes, such as learning and cognition. Additionally, the amygdala processes sensory information and relays this to other areas of the brain including the endocrine and autonomic domains of the hypothalamus and the brain stem. Thus, polynucleotides and polypeptides corresponding to this gene may also be useful for the detection and/or treatment of neural disorders that impact processes mediated by the amygdala. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0198]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:32 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2138 of SEQ ID NO:32, b is an integer of 15 to 2152, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:32, and where b is greater than or equal to a + 14.

**[0199] FEATURES OF PROTEIN ENCODED BY GENE NO: 23**

**[0200]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group: PPRPSTSGQWG (SEQ ID NO:311) and/or RRSPFTSAQTG (SEQ ID NO:312). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide

encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

[0201] The gene encoding the disclosed cDNA is thought to reside on chromosome 1. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 1.

[0202] When tested against SKNMC cell lines, supernatants removed from cells containing this gene activated the NFkB promoter element. Thus, it is likely that this gene activates neuroblastoma cells through the NFkB signal transduction pathway. NF-kB (Nuclear Factor kB) is a transcription factor activated by a wide variety of agents, leading to cell activation, differentiation, or apoptosis. Reporter constructs utilizing the NF-kB promoter element are used to screen supernatants for such activity.

[0203] This gene is expressed primarily in breast and soleus tissues, and, to a lesser extent, in several cell types, including T-cells.

[0204] Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, breast cancer, and musculo-skeletal diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the lactation system and breast, as well as the musculo-skeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., musculo-skeletal, breast, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one or both of the immunogenic epitopes shown in SEQ ID NO: 140 as residues: Thr-35 to Lys-43, Pro-

59 to Arg-64. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0205]** The tissue distribution in soleus tissue indicates that the protein product of this gene would be useful for the detection, treatment, and/or prevention of conditions and pathologies of the cardiovascular system, such as heart disease, restenosis, atherosclerosis, stroke, angina, thrombosis, and wound healing. Representative uses are described elsewhere herein. Likewise, expression in breast tissue indicates that polynucleotides and/or polypeptides of the invention would be useful for diagnosis, treatment and/or prevention of breast neoplasia and breast cancers, such as fibroadenoma, papillary carcinoma, ductal carcinoma, Paget's disease, medullary carcinoma, mucinous carcinoma, tubular carcinoma, secretory carcinoma and apocrine carcinoma, as well as juvenile hypertrophy and gynecomastia, mastitis and abscess, duct ectasia, fat necrosis and fibrocystic diseases. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0206]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:33 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1743 of SEQ ID NO:33, b is an integer of 15 to 1757, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:33, and where b is greater than or equal to a + 14.

**[0207] FEATURES OF PROTEIN ENCODED BY GENE NO: 24**

**[0208]** The gene encoding the disclosed cDNA is believed to reside on chromosome 3. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 3.

**[0209]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group:

GTGWDFGLAAVCLRAAEVAGSFK (SEQ ID NO:313),

GYRRVFEEYMRVISQRYPDIRIEGENYLPQPIYRHIASFLSVFKLVLIIGLIIVGK  
DPFAFFGMQAPSIWQWGQENKVYACMMVFFLSNMIENQCMSTGAFEITLND

VPVWSKLESGHLPSMQQLVQILDNEMKLNVMHDSIPHRS (SEQ ID NO:314),

GYRRVFEEYMRVISQRYPDIRIEGENYLPQPIYR (SEQ ID NO:315),

HIASFLSVFKLVLIIGLIIVGKDPFAFFGMQAPSI (SEQ ID NO:316),

WQWGQENKVYACMMVFFLSNMIENQCMSTGAFEI (SEQ ID NO:317),

TLNDVPVWSKLESGHLPSMQQLVQILDNEMKLNVMH (SEQ ID NO:318),

and/or DSIPHRS (SEQ ID NO: 298). Moreover, fragments and variants of these

polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these

polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are

encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0210]** This gene is expressed primarily in fast-growing tissues such as early development stage tissues, cancerous tissues, and hematopoietic tissues, and, to a lesser extent, in some other tissues.

**[0211]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, growth disorders, tumorigenesis, and immune and inflammatory disorders.

Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the fast-growing tissues such as early development stage tissues, cancer tissues, and

hematopoietic tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

[0212] The tissue distribution in fast-growing tissues such as early development stage tissues, cancerous tissues, and hematopoietic tissues, indicates that polynucleotides and polypeptides corresponding to this gene would be useful for detection, treatment, and/or prevention of growth disorders, tumorigenesis, and immune and inflammatory disorders. Similarly, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of cancer and other proliferative disorders. Expression in cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division. Additionally, the expression in hematopoietic cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene may play a role in the proliferation, differentiation, and/or survival of hematopoietic cell lineages. In such an event, polynucleotides and polypeptides corresponding to this gene may be useful in the treatment of lymphoproliferative disorders, and in the maintenance and differentiation of various hematopoietic lineages from early hematopoietic stem and committed progenitor cells. Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that polynucleotides and polypeptides corresponding to this gene may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired



immunodeficiency and certain degenerative disorders, such as spinal muscular atrophy (SMA). Alternatively, this gene product may be involved in the pattern of cellular proliferation that accompanies early embryogenesis. Thus, aberrant expression of this gene product in tissues - particularly adult tissues - may correlate with patterns of abnormal cellular proliferation, such as found in various cancers. Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention would be useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein would be useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0213]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:34 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1452 of SEQ ID NO:34, b is an integer of 15 to 1466, where both a and b correspond to the positions of

nucleotide residues shown in SEQ ID NO:34, and where b is greater than or equal to a + 14.

**[0214] FEATURES OF PROTEIN ENCODED BY GENE NO: 25**

**[0215]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

GRARGRPPGPEAAPASLSVSLRREVHSRGE (SEQ ID NO: 320). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0216]** The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 2 to about 18 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 19 to 130 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ib membrane proteins.

**[0217]** This gene is expressed primarily in olfactory epithelium and prostate.

**[0218]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, olfactory and prostate disorders and prostate cancer. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the olfactory system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., olfactory, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or

cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one or both of the immunogenic epitopes shown in SEQ ID NO: 142 as residues: His-24 to Ala-29, Glu-42 to Glu-49. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0219]** The tissue distribution primarily in the olfactory epithelium indicates a role for polynucleotides and polypeptides corresponding to this gene in the treatment, prevention, detection and/or diagnosis of olfactory and sensory disorders, including loss of the sense of smell. The expression in the prostate tissue indicates that polynucleotides and/or polypeptides of the invention would be useful for diagnosis, treatment and/or prevention of the disorders of the prostate, including inflammatory disorders, such as chronic prostatitis, granulomatous prostatitis and malacoplakia, prostatic hyperplasia and prostate neoplastic disorders, including adenocarcinoma, transitional cell carcinomas, ductal carcinomas, squamous cell carcinomas, or as hormones or factors with systemic or reproductive functions. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0220]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:35 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 512 of SEQ ID NO:35, b is an integer of 15 to 526, where both a and b correspond to the positions of

nucleotide residues shown in SEQ ID NO:35, and where b is greater than or equal to a + 14.

**[0221] FEATURES OF PROTEIN ENCODED BY GENE NO: 26**

**[0222]** The gene encoding the disclosed cDNA is believed to reside on chromosome 14. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 14.

**[0223]** This gene is expressed primarily in 8 week embryo.

**[0224]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly during fetal development, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., embryonic, cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0225]** The expression of this gene primarily in the embryo, indicates a key role for polynucleotides and polypeptides corresponding to this gene in embryo development and further indicates its usefulness in the treatment and/or detection of embryonic developmental defects. Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that polynucleotides and polypeptides corresponding to this gene may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental

tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain degenerative disorders, such as spinal muscular atrophy (SMA). Alternatively, polynucleotides and polypeptides corresponding to this gene may be involved in the pattern of cellular proliferation that accompanies early embryogenesis. Thus, aberrant expression of this gene product in tissues - particularly adult tissues - may correlate with patterns of abnormal cellular proliferation, such as found in various cancers. Because of potential roles in proliferation and differentiation, polynucleotides and polypeptides corresponding to this gene may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention would be useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The polynucleotides and polypeptides corresponding to this gene would be useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[0226] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:36 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence

would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2398 of SEQ ID NO:36, b is an integer of 15 to 2412, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:36, and where b is greater than or equal to a + 14.

**[0227] FEATURES OF PROTEIN ENCODED BY GENE NO: 27**

**[0228]** This gene is expressed primarily in neutrophils.

**[0229]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders affecting the immune system. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one or both of the immunogenic epitopes shown in SEQ ID NO: 144 as residues: Trp-25 to Thr-38, Pro-83 to Ala-88. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0230]** The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis, detection, prevention and/or treatment of immune system disorders, especially those affecting neutrophils. Furthermore, polynucleotides and polypeptides corresponding to this gene may be involved in the regulation of cytokine production, antigen presentation,

or other processes that may also suggest a usefulness in the treatment of cancer (e.g. by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, polynucleotides and polypeptides corresponding to this gene may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0231]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:37 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1260 of SEQ ID NO:37, b is an integer of 15 to 1274, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:37, and where b is greater than or equal to a + 14.

#### **[0232] FEATURES OF PROTEIN ENCODED BY GENE NO: 28**

**[0233]** The translation product of this gene shares sequence homology with protein complexes related to clathrin adaptors (see, e.g., AAD43327 (AF155157) which are thought to play a role in signal-mediated trafficking of integral membrane proteins in mammalian cells (see, e.g., Le Borgne and Hoflack, Curr Opin Cell Biol 10:499-503 (1998); all references available through this accession and reference are hereby incorporated by reference herein.) Based on the sequence similarity, the translation

product of this clone is expected to share at least some biological activities with protein complexes related to clathrin adaptors. Such activities are known in the art, some of which are described elsewhere herein.

**[0234]** The gene encoding the disclosed cDNA is thought to reside on chromosome 1. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 1.

**[0235]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

QTPFTCTLIHRHACXXPVRXSRVDPRVRGKQALIWLLGVHGERIPNAPYVLE  
DFVENVKSETFPAVKMELLTALLRLFLSRPAECQDMLGRLLYYCIEEEKDMA  
VRDRGLFYRLLL VGIDEVKRILCSPKSDPTLGLLEDPAERPVNSWASDFNTL  
VPVYGKAHWATISKCQGAERCDPELPKTSSFAASGPLIPEENKERVQELPSG  
ALMLVPNRQLTADYFEKTWLSLKVAHQQVLPWRGEFHPDTLQMALQVVNI  
QTIAMSRAGSRPWKAYLSAQDDTGCLFLTELLLEPGNSEMQISVKQNEARTE  
TLNSFISVLETVIGTIEEIKS (SEQ ID NO: 321) Moreover, fragments and variants

of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0236]** This gene is expressed primarily in fetal liver, immune cells (e.g., eosinophils and T-cells), colon tumor, and brain tissue, and, to a lesser extent, in various other fetal and transformed cell types.

**[0237]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune, developmental and neurological conditions. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing, immune and



central nervous systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, developing, neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one, two, three, four, five or all six of the immunogenic epitopes shown in SEQ ID NO: 145 as residues: Pro-75 to Asn-81, Gln-106 to Cys-111, Glu-130 to Asp-141, Arg-176 to Asp-182, Ala-201 to Trp-206, Lys-238 to Thr-246. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

[0238] The tissue distribution in fetal liver and brain tissues indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the study, detection, diagnosis, prevention and/or treatment of growth disorders and neoplasias of the immune and central nervous systems. The tissue distribution indicates polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition,

homeostasis, or neuronal differentiation or survival. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Alternatively, expression of this gene product in fetal liver/spleen tissue indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. Polynucleotides and polypeptides of the invention may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[0239] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:38 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1022 of SEQ ID NO:38, b is an integer of 15 to 1036, where both a and b correspond to the positions of

nucleotide residues shown in SEQ ID NO:38, and where b is greater than or equal to a + 14.

**[0240] FEATURES OF PROTEIN ENCODED BY GENE NO: 29**

**[0241]** This gene shares sequence homology to fibulin (see, e.g., GeneSeq Accession No. R11148 and R11149; all references available through these accessions are hereby incorporated in their entirety by reference herein). Fibulin binds to the cytoplasmic domain of the beta-1 subunit of integrin adhesion receptors in a cation-dependent, EDTA-reversible manner. Thus, polynucleotides and polypeptides of the invention may be used to manipulate adhesion of cells to fibronectin, collagen, laminin, and possibly also other proteins.

**[0242]** When tested against both U937 Myeloid cell lines and Jurkat T-cell cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that this gene activates both T-cells and myeloid cells, and to a lesser extent other tissues and cell types, through the Jak-STAT signal transduction pathway. The gamma activating sequence (GAS) is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

**[0243]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence: CENTEGGYRCIC (SEQ ID NO:322). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention. This sequence contains an aspartic acid and asparagine hydroxylation site of the consensus sequence:

C.[DN].{4}[FY].C.C (D or N is the hydroxylation site). Post-translational hydroxylation of aspartic acid or asparagine to form erythro-beta-hydroxyaspartic acid or erythro-beta-hydroxyasparagine has been identified in a number of proteins with domains homologous to epidermal growth factor (EGF) (see, e.g., Stenflo J., et al., J. Biol. Chem. 263:21-24 (1988)). Examples of such proteins are the blood coagulation protein factors VII, IX and X, proteins C, S, and Z, the LDL receptor, thrombomodulin, etc. Based on sequence comparisons of the EGF-homology region that contains hydroxylated Asp or Asn, a consensus sequence has been identified that seems to be required by the hydroxylase(s). All references are hereby incorporated in their entirety herein by reference.

[0244] In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group: CDCQAGYGGGEAC (SEQ ID NO: 323) and/or CICAEGYKQMEGIC (SEQ ID NO: 324). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention. These sequences contain EGF-like domain signatures (consensus sequence: C.C.{5}G.{2}C or C.C.{2}[GP][FYW].{4,8}C). A sequence of about thirty to forty amino-acid residues long found in the sequence of epidermal growth factor (EGF) has been shown to be present, in a more or less conserved form, in a large number of other, mostly animal proteins. The functional significance of EGF domains in what appear to be unrelated proteins is not yet clear. However, a common feature is that these repeats are found in the extracellular domain of membrane-bound proteins or in proteins known to be secreted. For further information see, e.g., Davis C.G., New Biol. 2:410-419 (1990), Blomquist M.C., et al., Proc. Natl. Acad. Sci. U.S.A. 81:7363-7367 (1984), Barker W.C., et al., Protein Nucl. Acid Enz. 29:54-68 (1986), Doolittle R.F., et al., Nature 307:558-560 (1984), Appella E., et al., FEBS Lett. 231:1-4 (1988), Campbell I.D., et al., Curr. Opin.

Struct. Biol. 3:385-392 (1993), and/or Tamkun J.W., et al., Cell 46:271-282 (1986).

All references are hereby incorporated in their entirety herein by reference.

**[0245]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group: DIDECGTEGANCGADQFCVNTEGSYEC (SEQ ID NO: 325) and/or DVDECETEVCPGENKQCENTEGGYRC (SEQ ID NO: 326). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention. These sequences contain Calcium-binding EGF-like domain pattern signatures (consensus sequence:

[DEQN].[DEQN]{2}C.{3,14}C.{3,7}C.[DN].{4}[FY].C). A sequence of about forty amino-acid residues long found in the sequence of epidermal growth factor (EGF) has been shown to be present in a large number of membrane-bound and extracellular, mostly animal proteins. Many of these proteins require calcium for their biological function and a calcium-binding site has been found to be located at the N-terminus of some EGF-like domains. Calcium-binding may be crucial for numerous protein-protein interactions. Some proteins that are known or that are predicted to contain calcium-binding EGF-like domains include: Bone morphogenic protein 1 (BMP-1), Calcium-dependent serine proteinase (CASP), Cartilage oligomeric matrix protein COMP, Coagulation factors VII, IX, and X, Fibrillin 1 and fibrillin 2, and Leucocyte antigen. For references see: New Biol. 2:410-419 (1990), Blomquist M.C., et al., Proc. Natl. Acad. Sci. U.S.A. 81:7363-7367 (1984), Barker W.C., et al., Protein Nucl. Acid Enz. 29:54-68 (1986), Doolittle R.F., et al., Nature 307:558-560 (1984), Appella E., et al., FEBS Lett. 231:1-4 (1988) Campbell I.D., et al., Curr. Opin. Struct. Biol. 3:385-392 (1993), Rao Z., et al., Cell 82:131-141 (1995), et al., J. Biol. Chem. 267:19642-19649 (1992). All references are hereby incorporated in their entirety herein by reference.

**[0246]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

CDCQAGYGGEACGQCGLGYFEAERNASHLVCSAC (SEQ ID NO: 327).

Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention. This sequence contains a Laminin-type EGF-like (LE) domain signature (consensus sequence: C-x(1,2)-C-x(5)-G-x(2)-C-x(2)-C-x(3,4)-[FYW]-x(3,15)-C). Laminins (see, e.g., Beck K., et al., FASEB J. 4:148-160(1990)) are the major noncollagenous components of basement membranes that mediate cell adhesion, growth migration, and differentiation. They are composed of distinct but related alpha, beta and gamma chains. The three chains form a cross-shaped molecule that consist of a long arm and three short globular arms. The long arm consist of a coiled coil structure contributed by all three chains and cross-linked by interchain disulfide bonds. Beside different types of globular domains each subunit contains, in its first half, consecutive repeats of about 60 amino acids in length that include eight conserved cysteines (see, e.g., Engel J., FEBS Lett. 251:1-7(1989)). The tertiary structure (see, e.g., Stetefeld J., et al., J. Mol. Biol. 257:644-657(1996) Baumgartner R., et al., J. Mol. Biol. 257:658-668(1996)) of this domain is remotely similar in its N-terminal to that of the EGF-like module. It is known as a 'LE' or 'laminin-type EGF-like' domain. The number of copies of the LE domain in the different forms of laminins is highly variable; from 3 up to 22 copies have been found. All references are hereby incorporated in their entirety herein by reference.

**[0247]** The gene encoding the disclosed cDNA is thought to reside on chromosome 3. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 3.

**[0248]** This gene is expressed primarily in cerebellum tissue, and, to a lesser extent, in multiple tissues and cell types including prostate, liver, T-cells, kidney, and lung

tissues, as well as musculo-skeletal tissues such as endothelial tissue, healing groin wound tissue, fetal heart tissue, and osteosarcoma tissue.

**[0249]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders of the central nervous system, including dementia, mood disorders, both unipolar and bipolar depression, and Alzheimer's disease, as well as disorders of the musculo-skeletal, renal, and pulmonary systems. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, renal, pulmonary system, and musculo-skeletal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, musculo-skeletal, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one, two, three, four, five, six, seven, eight, nine ten, eleven, twelve, thirteen, fourteen, or all fifteen of the immunogenic epitopes shown in SEQ ID NO: 146 as residues: Pro-28 to Thr-45, Arg-59 to Gly-67, Ala-71 to Glu-84, Lys-120 to Asp-126, Pro-159 to Gly-164, Glu-167 to Gly-186, Arg-217 to Asn-225, Glu-245 to Ala-255, Gly-282 to Gly-297, Pro-312 to Gly-324, Thr-356 to Lys-364, Gly-366 to Thr-372, Lys-377 to Ala-383, Gly-397 to Thr-407, Thr-419 to Gly-433. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0250]** The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis, detection, prevention and/or treatment of a variety of cancers, most notably cancers of the central nervous system, pulmonary, and renal systems, as well as the disorders of the central nervous

system listed above. Representative uses are described in the "Hyperproliferative Diseases", "Chemotaxis" and "Binding Activity" sections below, in Examples 11, 12, 13, 14, 15, 16, 18, 19, and 20, and elsewhere herein. Briefly, the expression of this gene product in a variety of systems indicates that polynucleotides and polypeptides corresponding to this gene may be a player in the progression of these diseases, and may be a beneficial target for inhibitors as therapeutics. Alternatively, the tissue distribution in musculo-skeletal tissues, as the homology to fibulin, indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, diagnosis, prevention and/or treatment of disorders involving the vasculature. Elevated expression of this gene product by endothelial cells indicates that it may play vital roles in the regulation of endothelial cell function; secretion; proliferation; or angiogenesis. Alternately, this may represent a gene product expressed by the endothelium and transported to distant sites of action on a variety of target organs. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0251]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:39 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1365 of SEQ ID NO:39, b is an integer of 15 to 1379, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:39, and where b is greater than or equal to a + 14.

#### **[0252] FEATURES OF PROTEIN ENCODED BY GENE NO: 30**



[0253] The translation product of this gene shares sequence homology with coxsackie and adenovirus receptor in mouse. Particularly, this gene shares sequence homology with a human A33 antigen, which is a transmembrane protein and a novel member of the immunoglobulin superfamily. (see, e.g., Proc. Natl. Acad. Sci. U.S.A. 94, 469-474 (1997); see also, Accession No. 1814277; all references available through the accession and reference are hereby incorporated herein by reference.) Therefore, this gene likely has activity similar to the human A33 antigen.

[0254] In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group:

MISLPGPLVTNLLRFLFLGLSALAPPSRAQLQLHLPANRLQAVEGGEVVLPAW  
YTLHGEVSSSQPWEVPFVMWFFKQKEKEDQVLSYINGVTTSKPGVSLVYSMP  
SRNLSLRLEGLQEKDSGPYSCSVNVQNKQGKSRGHSIKTLELNVLVPPAPPSC  
RLQGVPHVGANVTLSQCSPRSKPAVQYQWDRQLPSFQTFAPALDVIRGSLS  
LTNLSSSMAGVYVCKAHNEVGTAQCNVTLEVSTGPGAAGVAVVAGAVVGTLVG  
LGLLAGLVLLYHRRGKALEEPANDIKEDAIAPRTLTPWKSSDTISKNGTLSSV  
TSARALRPPHGP RP GALTPTPSLSSQALPSRLPTTDGAHPQPISPIPGGVSSSG  
LSRMGAVPVMVPAQSQAGSL (SEQ ID NO:328),

MISLPGPLVTNLLRFLFLGLSALAPPSRAQLQLHL (SEQ ID NO:329),

PANRLQAVEGGEVVLPAWYTLHGEVSSSQPWEVPF (SEQ ID NO:330),

VMWFFKQKEKEDQVLSYINGVTTSKPGVSLVYSMP (SEQ ID NO:331),

SRNLSLRLEGLQEKDSGPYSCSVNVQNKQGKSRGH (SEQ ID NO:332),

SIKTLELNVLVPPAPPSCRLQGVPHVGANVTLSQC (SEQ ID NO:333),

SPRSKPAVQYQWDRQLPSFQTFAPALDVIRGSLS (SEQ ID NO:334),

LTNLSSSMAGVYVCKAHNEVGTAQCNVTLEVSTGP (SEQ ID NO:335),

GAAVVAGAVVGTLVGLGLLAGLVLLYHRRGKALEE (SEQ ID NO:336),

PANDIKEDAIAPRTLTPWKSSDTISKNGTLSSVTS (SEQ ID NO:337),

ARALRPPHGP RP GALTPTPSLSSQALPSRLPTT (SEQ ID NO:338), and/or

DGAHPQPISPIPGGVSSSGLSRMGAVPVMVPAQSQAGSL (SEQ ID NO:339).

Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by

a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0255]** The translated product of this gene also shares some homology with a mouse basement membrane proteoglycan (see, e.g., GenBank Accession AAA39911.1 and Noonan,D.M., et al., J. Biol. Chem. 266, 22939-22947 (1991); all references available through this citation are hereby incorporated herein by reference). Based on the sequence similarity, the translation product of this clone is expected to share at least some biological activities with extracellular basement membrane proteoglycans. Such activities are known in the art, some of which are described elsewhere herein.

**[0256]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

LSLTNLSSSMAGVYVCKAHNEVGTAQCNVTLEVSTG (SEQ ID NO: 340).

Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0257]** Contact of cells with supernatant expressing the product of this gene has been shown to increase the permeability of the plasma membrane of THP-1 cell lines to calcium. Thus it is likely that the product of this gene is involved in a signal transduction pathway that is initiated when the product binds a receptor on the surface of the plasma membrane of both monocytes, and to a lesser extent, other immune and hematopoietic cells. Thus, polynucleotides and polypeptides have uses which include, but are not limited to, activating monocytes. Binding of a ligand to a receptor is known to alter intracellular levels of small molecules, such as calcium, potassium and sodium, as well as alter pH and membrane potential. Alterations in small molecule

concentration can be measured to identify supernatants which bind to receptors of a particular cell.

**[0258]** This gene is expressed in various tissues including placenta, brain, heart, muscle, adipocytes, and liver.

**[0259]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions: viral diseases, and immune diseases and/or disorders. Similarly, polypeptides and antibodies directed to those polypeptides would be useful to provide immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., CNS, reproductive, vascular, cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0260]** The tissue distribution in various tissues including placenta, brain, heart, muscle, adipocytes, and liver, and the homology to A33 antigen indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis, detection, prevention and/or treatment of a variety of cancers, most notably cancers of the immune system, as well as viral infections. Expression of this gene product indicates that polynucleotides and polypeptides corresponding to this gene may be a player in the progression of these diseases, and may be a beneficial target for inhibitors as therapeutics. Representative uses are described in the “Chemotaxis” and “Binding Activity” sections below, in Examples 11, 12, 13, 14, 15, 16, 18, 19, and 20, and elsewhere herein. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may

show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0261]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:40 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1918 of SEQ ID NO:40, b is an integer of 15 to 1932, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:40, and where b is greater than or equal to a + 14.

**[0262] FEATURES OF PROTEIN ENCODED BY GENE NO: 31**

**[0263]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group: GSSFVVSEGSYLDISDWLNPAKLSLYY (SEQ ID NO:341), LDISDWLNPAKL (SEQ ID NO:342), SDWLNPAKLSL (SEQ ID NO:343), and/or DACEQLCDPETGE (SEQ ID NO:344). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0264]** This gene is expressed primarily in human ovary and adrenal gland tissues.

**[0265]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive diseases and/or disorders, particularly ovarian cancer. Similarly,

polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

[0266] The tissue distribution in ovary tissue indicates that polynucleotides and polypeptides corresponding to this gene would be useful for diagnosing and/or treating reproductive system disorders including ovarian cancer, as well as cancers of other tissues where expression has been observed. Representative uses are described in the “Hyperproliferative Disorders” and “Regeneration” sections below and elsewhere herein. Expression in ovarian tissue, indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the treatment, prevention, detection and diagnosis of conditions concerning proper ovarian function (e.g., egg maturation, endocrine function), as well as cancer. The expression in ovarian tissue may indicate the gene or its products can be used to treat, prevent, detect and/or diagnose disorders of the ovary, including inflammatory disorders, such as oophoritis (e.g., caused by viral or bacterial infection), ovarian cysts, amenorrhea, infertility, hirsutism, and ovarian cancer (including, but not limited to, primary and secondary cancerous growth, endometrioid carcinoma of the ovary, ovarian papillary serous adenocarcinoma, ovarian mucinous adenocarcinoma, Ovarian Krukenberg tumor). Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0267]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:41 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1416 of SEQ ID NO:41, b is an integer of 15 to 1430, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:41, and where b is greater than or equal to a + 14.

**[0268] FEATURES OF PROTEIN ENCODED BY GENE NO: 32**

**[0269]** This gene is expressed primarily in thymus and stromal cells.

**[0270]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, aberrant immune responses, such as either chronic or acute inflammation.

Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0271]** The tissue distribution in thymus stromal cells indicates that polynucleotides and polypeptides corresponding to this gene would be useful for diagnosing, detecting, preventing and/or treating disorders of the immune system, particularly those involving a pathological inflammatory response. Representative uses are

described in the “Immune Activity” and “Infectious Disease” sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Furthermore, the gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, polynucleotides and polypeptides corresponding to this gene may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[0272] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:42 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1393 of SEQ ID NO:42, b is an integer of 15 to 1407, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:42, and where b is greater than or equal to a + 14.

#### **[0273] FEATURES OF PROTEIN ENCODED BY GENE NO: 33**

[0274] In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

EGKIKICEKKAIVILHTCNS (SEQ ID NO: 345). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes,

under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0275]** This gene is expressed primarily in frontal cortex.

**[0276]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, central nervous system (CNS) diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the CNS, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., brain, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or cerebrospinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of the immunogenic epitopes shown in SEQ ID NO: 150 as residues: Pro-41 to Asp-47. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0277]** The tissue distribution in frontal cortex indicates that polynucleotides and polypeptides corresponding to this gene would be useful for detection, treatment, and/or prevention of CNS disorders including disorders of the brain and nervous system. Representative uses are described in the “Regeneration” and “Hyperproliferative Disorders” sections below, in Example 11, 15, and 18, and elsewhere herein. Elevated expression of this gene product within the frontal cortex of the brain indicates that it may be involved in neuronal survival, synapse formation, conductance, neural differentiation, etc. Such involvement may impact many processes, such as learning and cognition. It may also be useful in the treatment of such neurodegenerative disorders as schizophrenia, ALS, or Alzheimer's.



Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0278]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:43 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 936 of SEQ ID NO:43, b is an integer of 15 to 950, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:43, and where b is greater than or equal to a + 14.

#### **[0279] FEATURES OF PROTEIN ENCODED BY GENE NO: 34**

**[0280]** This gene is expressed primarily in adipose tissue, human embryo, and neutrophils.

**[0281]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, obesity, Nasu-Hakola disease, cardiovascular disease, non-insulin-dependent diabetes mellitus. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the adipose, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., adipose, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an

individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0282]** The tissue distribution in adipose indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the treatment, prevention, detection and diagnosis of metabolic disorders related to lipids and adipose tissue, such as obesity, Nasu-Hakola disease (membranous lipodystrophy), cardiovascular disease, lipidemia, non-insulin-dependent diabetes mellitus, stroke and carcinoma. The tissue distribution in neutrophils indicates polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. Involvement in the regulation of cytokine production, antigen presentation, or other processes indicates a usefulness for treatment of cancer (e.g., by boosting immune responses). Expression in cells of lymphoid origin, indicates the natural gene product would be involved in immune functions. Therefore it would also be useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, polynucleotides and polypeptides corresponding to this gene are thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or

proliferation of various cell types. Moreover, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that polynucleotides and polypeptides corresponding to this gene may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain degenerative disorders, such as spinal muscular atrophy (SMA). Alternatively, this gene product may be involved in the pattern of cellular proliferation that accompanies early embryogenesis. Thus, aberrant expression of this gene product in tissues - particularly adult tissues - may correlate with patterns of abnormal cellular proliferation, such as found in various cancers. Because of potential roles in proliferation and differentiation, this gene product may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention would be useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus polynucleotides and polypeptides corresponding to this gene may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The polynucleotides and polypeptides corresponding to this gene would be useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as,

antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0283]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:44 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 990 of SEQ ID NO:44, b is an integer of 15 to 1004, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:44, and where b is greater than or equal to a + 14.

**[0284] FEATURES OF PROTEIN ENCODED BY GENE NO: 35**

**[0285]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

NSARVEFFIPPLRITQKVRSTKS (SEQ ID NO:346). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0286]** This gene is apparently expressed primarily in IL-1- and LPS-induced neutrophils.

**[0287]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, abnormal immune reactions or disorders including, but not limited to, chronic or cyclic neutropenia, neutrophilia, and neutrocytosis. Similarly, polypeptides and

antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

[0288] The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene would be useful for detection, treatment, and/or prevention of immune disorders or abnormal reactions mediated by neutrophils, including infection, inflammation, allergy, immunodeficiency, chronic or cyclic neutropenia, neutrophilia, and neutrocytosis, and the like. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Moreover, the expression of this gene product indicates a role in regulating the proliferation, survival, differentiation, and/or activation of hematopoietic cell lineages, including blood stem cells. Polynucleotides and polypeptides corresponding to this gene may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity, immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. In

addition, polynucleotides and polypeptides corresponding to this gene may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0289]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:45 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1667 of SEQ ID NO:45, b is an integer of 15 to 1681, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:45, and where b is greater than or equal to a + 14.

**[0290] FEATURES OF PROTEIN ENCODED BY GENE NO: 36**

**[0291]** The translated ORF of the contig has homology with the human, porcine, and bovine INS10 double-chain insulin precursor, especially around a region containing multiple cysteine residues.

**[0292]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group:

MMVWNLFPFCFPPLLLLQFIDCQQSSEIEQGFTSRLLGHPIFFCPDPCWQSCMN  
CVILSVLSFFFILRWISKIVAVQKLESSRRKPILFLIISCEIASFIHLFLSQMSAEC  
CCFYLVILICKY (SEQ ID NO:347), MMVWNLFPFCFPPLLLLQFIDCQQSSEIE  
(SEQ ID NO:348), QGFTSRLLGHPIFFCPDPCWQSCMNCVI (SEQ ID NO:349),  
LSVLSFFFILRWISKIVAVQKLESSRRKPILFLI (SEQ ID NO:350), and/or

ISCEIASFIHLFLSQMSAECCCFYLVILICKY (SEQ ID NO:351). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0293]** The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 50 to about 66 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 67 to 90 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ia membrane proteins.

**[0294]** The gene encoding the disclosed cDNA is believed to reside on chromosome 21. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 21.

**[0295]** This gene is expressed primarily in cells and tissues isolated from a 15 days post-incision healing abdomen wound and, to a lesser extent, in many immune tissues (e.g., T-cells and B-cells) and connective tissues/cells with proliferative capacity, such as osteoclastoma, ovarian cancer, B-cell lymphoma and hepatocellular tumor.

**[0296]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, wound healing, diabetes mellitus, and cancers of the bone and connective tissues, lymphomas, and cancers of the liver. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly those of the cells and tissues involved in healing tissue damages and regeneration, diabetes mellitus, and many cancers including, but not limited to ovarian cancer, breast cancer, colon cancer, cardiac

tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, and the like, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one, or both of the immunogenic epitopes shown in SEQ ID NO: 153 as residues: Gln-22 to Phe-31, Leu-78 to Lys-85. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0297]** The tissue distribution in healing wound and regenerating tissues/cells indicates that polynucleotides and polypeptides corresponding to this gene would be useful for detection, treatment, and/or prevention of tissue damages, trauma, necrosis, and tissue regeneration. In addition, since this gene exhibits homology with an insulin precursor, polynucleotides and polypeptides corresponding to this gene can be used to regulate the metabolism of glucose or other sugars, the synthesis of proteins, and the formation and storage of neutral lipids. The tissue distribution in immune tissues (e.g., T-cells and B-cells) indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. Involvement in the regulation of cytokine production, antigen presentation, or other processes indicates a usefulness for treatment of cancer (e.g., by boosting immune responses). Expression in cells of lymphoid origin, indicates the natural gene product would be involved in immune



functions. Therefore polynucleotides and polypeptides corresponding to this gene would also be useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma.

Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, polynucleotides and polypeptides corresponding to this gene are thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0298]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:46 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1347 of SEQ ID NO:46, b is an integer of 15 to 1361, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:46, and where b is greater than or equal to a + 14.

**[0299] FEATURES OF PROTEIN ENCODED BY GENE NO: 37**

**[0300]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

KVDTPRRHFCPEISFFLTPLPQSARNSTVRNALSGLKNLTPAMISTVSKQDTSK  
LGEEE (SEQ ID NO:352). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0301]** When tested against U937 Myeloid cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that this gene activates myeloid cells through the Jak-STAT signal transduction pathway. The gamma activating sequence (GAS) is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

**[0302]** The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 7 to about 23 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 24 to 105 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type Ia membrane proteins.

**[0303]** This gene is expressed primarily in B-cell lymphoma.

**[0304]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, B-cell lymphoma, immunodeficient or auto-immune conditions. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in

providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0305]** The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of B-cell lymphomas, as well as other immune disorders including: leukemias, auto-immunities, immunodeficiencies (e.g., AIDS), immuno-suppressive conditions (transplantation) and hematopoietic disorders, such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia, since stromal cells are important in the production of cells of hematopoietic lineages. In addition, polynucleotides and polypeptides corresponding to this gene may be applicable in conditions of general microbial infection, inflammation or cancer. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. The uses include bone marrow cell ex vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The polynucleotides and polypeptides corresponding to this gene may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, the biological activity of supernatants from cells expressing this gene in the GAS assay indicates that this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0306]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:47 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1123 of SEQ ID NO:47, b is an integer of 15 to 1137, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:47, and where b is greater than or equal to a + 14.

**[0307] FEATURES OF PROTEIN ENCODED BY GENE NO: 38**

**[0308]** The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 8 to about 24 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino acids 1 to 7 of this protein has also been determined. Based upon these characteristics, it is believed that the protein product of this gene shares structural features to type II membrane proteins.

**[0309]** The gene encoding the disclosed cDNA is thought to reside on chromosome 10. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 10.

**[0310]** This gene is expressed primarily in infant brain, testes, brain, osteoblasts, and caudate nucleus tissues, and, to a lesser extent, in various other normal and transformed cell types, including smooth muscle and adult heart tissues, and T-cell lymphoma.

**[0311]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological and growth defects. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing nervous system, expression of this gene

at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0312]** The tissue distribution in infant brain tissue indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the study, detection and/or treatment of infant and general nervous system disorders and neoplasias. The tissue distribution indicates polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Moreover, the tissue distribution in immune cells (e.g., T-cells) indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis, detection, prevention and/or treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious

Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. Involvement in the regulation of cytokine production, antigen presentation, or other processes indicates a usefulness for treatment of cancer (e.g., by boosting immune responses). Expression in cells of lymphoid origin, indicates the natural gene product would be involved in immune functions. Therefore it would also be useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0313]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:48 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the

general formula of a-b, where a is any integer between 1 to 2749 of SEQ ID NO:48, b is an integer of 15 to 2763, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:48, and where b is greater than or equal to a + 14.

**[0314] FEATURES OF PROTEIN ENCODED BY GENE NO: 39**

**[0315]** The translated product of this gene shares some homology with a *Caenorhabditis elegans* gene product containing zinc finger-like motifs (see, e.g., Genbank Accession No.: AAA91223 and Wilson, R., et al., Nature 368, 32-38 (1994)). Similarly, the translated product of this gene also shares some homology with transcriptional regulatory proteins from *Saccharomyces cerevisiae* (see, e.g., GenBank Accessions Nos.: CAA92346.1, BAA04890.1, and AAA34471.1). All references available through the above listed accessions and citations are hereby incorporated herein by reference. Based on the sequence similarity, the translation product of this clone is expected to share at least some biological activities with transcriptional regulatory proteins. Such activities are known in the art, some of which are described elsewhere herein.

**[0316]** This gene is expressed primarily in epithelial-TNF $\alpha$  and INF induced cells and brain frontal cortex.

**[0317]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., CNS, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or

bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one or both of the immunogenic epitopes shown in SEQ ID NO: 156 as residues: Lys-35 to Asp-41, Glu-49 to Leu-63. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0318]** The tissue distribution in the brain indicates that polynucleotides and polypeptides corresponding to this gene would be useful for detection, treatment, and/or prevention of neurodegenerative disorders, especially those involving the frontal cortex. Representative uses are described in the “Regeneration” and “Hyperproliferative Disorders” sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the elevated expression of this gene product within the frontal cortex of the brain indicates that it may be involved in neuronal survival; synapse formation; conductance; neural differentiation, etc. Such involvement may impact many processes, such as learning and cognition. Polynucleotides and polypeptides corresponding to this gene may also be useful in the treatment of such neurodegenerative disorders as schizophrenia; ALS; or Alzheimer's. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0319]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:49 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1334 of SEQ ID NO:49, b is an integer of 15 to 1348, where both a and b correspond to the positions of



nucleotide residues shown in SEQ ID NO:49, and where b is greater than or equal to a + 14.

**[0320] FEATURES OF PROTEIN ENCODED BY GENE NO: 40**

**[0321]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

PTRPPTRPLSFTFTKQTSSTCLSLHF (SEQ ID NO:353). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0322]** The gene encoding the disclosed cDNA is believed to reside on chromosome 18. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 18.

**[0323]** This gene is expressed primarily in infant brain, frontal cortex, and, to a lesser extent, in melanocytes.

**[0324]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., CNS, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the

present invention comprise, or alternatively consist of one or both of the immunogenic epitopes shown in SEQ ID NO: 157 as residues: Val-40 to Cys-47, Lys-49 to Gly-54. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

[0325] The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of neurodegenerative disorders especially those involving the frontal cortex. Moreover, polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, polynucleotides and polypeptides corresponding to this gene are involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[0326] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:50 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1250 of SEQ ID NO:50, b is an integer of 15 to 1264, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:50, and where b is greater than or equal to a + 14.

**[0327] FEATURES OF PROTEIN ENCODED BY GENE NO: 41**

**[0328]** This gene shows structural homology with the duck insulin precursor which is thought to be important in metabolic homeostasis. (see, e.g., Genbank Accession No. pir|A01600|IPDK insulin precursor; all references available through this accession number are hereby incorporated in their entirety by reference herein).

**[0329]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

LECVLLICFRAMSAIYTHTSIGNAQLFTDGSFRRVREPLPKEGKSWPQ  
(SEQ ID NO: 354). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0330]** This gene is expressed primarily in eosinophil-IL5 induced cells, and, to a lesser extent, in B cell lymphoma, breast lymph node, and CD34 depleted buffy coat (cord blood).

**[0331]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune diseases and/or disorders. Similarly, polypeptides and antibodies directed

to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise immunogenic epitopes shown in SEQ ID NO: 158 as residues: Arg-39 to Glu-56. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0332]** The tissue distribution in hematopoietic tissues indicates that polynucleotides and polypeptides corresponding to this gene would be useful for detection, treatment, and/or prevention of immune disorders especially those involving eosinophils and B-cells. Polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. Polynucleotides and polypeptides corresponding to this gene may be involved in the regulation of cytokine production, antigen presentation, or other processes suggesting a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the natural gene product may be involved in immune functions. Therefore polynucleotides and polypeptides of the invention may be also used as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis,

hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, scleroderma and tissues. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. In addition, polynucleotides and polypeptides corresponding to this gene may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[0333] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:51 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1646 of SEQ ID NO:51, b is an integer of 15 to 1660, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:51, and where b is greater than or equal to a + 14.

#### **[0334] FEATURES OF PROTEIN ENCODED BY GENE NO: 42**

[0335] In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

KQNLTNLDVPVQYHVALSDKVK (SEQ ID NO: 355). Moreover, fragments and

variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

[0336] This gene is expressed primarily in pineal gland and, to a lesser extent, in multiple sclerosis cells.

[0337] Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, insomnia, multiple sclerosis, and other neurodegenerative diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system and endocrine system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., CNS, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of the immunogenic epitopes shown in SEQ ID NO: 159 as residues: Pro-7 to Gly-12. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

[0338] The tissue distribution primarily in pineal gland and, to a lesser extent, in multiple sclerosis cells indicates that polynucleotides and polypeptides corresponding to this gene would be useful for treatment of insomnia and jet lag through agonist or antagonist interaction with pineal gland receptors to allow regulation of melatonin production. Representative uses are described elsewhere herein. This gene may also

be useful in the treatment of multiple sclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[0339] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:52 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1664 of SEQ ID NO:52, b is an integer of 15 to 1678, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:52, and where b is greater than or equal to a + 14.

#### **[0340] FEATURES OF PROTEIN ENCODED BY GENE NO: 43**

[0341] The gene encoding the disclosed cDNA is believed to reside on chromosome 2. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 2.

[0342] In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

PSCPPPEMKKELPVDSCLPRLSLELHPQKMDPKRQHIQLLSSLTECLTVDPLSASV  
WRQLYPKHLSQSSLLLXHLLSSWEQIPKKVQKSLQETIQLKLTNQELLRKGS  
SNNQDVVTCD (SEQ ID NO: 356). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are

encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

[0343] When tested against Jurket and U937 cell lines, supernatants removed from cells containing this gene activated the NFkB promoter element. Thus, it is likely that this gene activates T-cells and myeloid cells through the NFkB signal transduction pathway. NF-kB (Nuclear Factor kB) is a transcription factor activated by a wide variety of agents, leading to cell activation, differentiation, or apoptosis. Reporter constructs utilizing the NF-kB promoter element are used to screen supernatants for such activity.

[0344] This gene is expressed primarily in ovary tumors and breast cancer and, to a lesser extent, in normal lung and colon tumors.

[0345] Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, cancer, particularly of the ovary and breast; and colon. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the colon, breast, or female reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, gastrointestinal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

[0346] The tissue distribution primarily in ovary tumors and breast cancer and, to a lesser extent, in normal lung and colon tumors indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis and/or treatment of a variety of cancers, most notably cancers of the ovary, breast, or colon. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, the expression of



polynucleotides and polypeptides corresponding to this gene in a variety of cancers indicates that it may be a player in the progression of the disease, and may be a beneficial target for inhibitors as therapeutics. Similarly, expression in ovarian tissue, indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the treatment, prevention, detection and diagnosis of conditions concerning proper ovarian function (e.g., egg maturation, endocrine function), as well as cancer. The expression in ovarian tissue may indicate the gene or its products can be used to treat, prevent, detect and/or diagnose disorders of the ovary, including inflammatory disorders, such as oophoritis (e.g., caused by viral or bacterial infection), ovarian cysts, amenorrhea, infertility, hirsutism, and ovarian cancer (including, but not limited to, primary and secondary cancerous growth, endometrioid carcinoma of the ovary, ovarian papillary serous adenocarcinoma, ovarian mucinous adenocarcinoma, Ovarian Krukenberg tumor). Likewise, expression in breast tissue indicates that polynucleotides and/or polypeptides of the invention would be useful for diagnosis, treatment and/or prevention of breast neoplasia and breast cancers, such as fibroadenoma, papillary carcinoma, ductal carcinoma, Paget's disease, medullary carcinoma, mucinous carcinoma, tubular carcinoma, secretory carcinoma and apocrine carcinoma, as well as juvenile hypertrophy and gynecomastia, mastitis and abscess, duct ectasia, fat necrosis and fibrocystic diseases. The tissue distribution in colon and colon cancer indicates that polynucleotides and polypeptides corresponding to this gene would be useful for diagnosis, treatment, prevention and/or detection of tumors, especially of the intestine, such as, carcinoid tumors, lymphomas, non-neoplastic polyps, adenomas, familial syndromes, colorectal carcinogenesis, colorectal carcinoma, cancer of the colon, cancer of the rectum and carcinoid tumors, as well as cancers in other tissues where expression has been indicated. The expression in the colon tissue may indicate that polynucleotides and polypeptides of the invention can be used to treat, detect, prevent and/or diagnose disorders of the colon, including inflammatory disorders such as, congenital abnormalities, such as atresia and stenosis, Meckel diverticulum, congenital aganglionic megacolon-Hirschsprung disease; enterocolitis, such as diarrhea and dysentery, infectious enterocolitis, including viral gastroenteritis, bacterial enterocolitis, necrotizing

enterocolitis, antibiotic-associated colitis (pseudomembranous colitis), and collagenous and lymphocytic colitis, miscellaneous intestinal inflammatory disorders, including parasites and protozoa, amoebic colitis, acquired immunodeficiency syndrome, transplantation, drug-induced intestinal injury, radiation enterocolitis, neutropenic colitis, diverticular colon disease (DCD), inflammatory colonic disease, idiopathic inflammatory bowel disease, such as Crohn's disease (CD), non-inflammatory bowel disease (non-IBD) colonic inflammation; ulcerative disorders such as, ulcerative colitis (UC); eosinophilic colitis; noncancerous tumors, such as, polyps in the colon, adenomas, leiomyomas, lipomas, and angiomas. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[0347] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:53 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1846 of SEQ ID NO:53, b is an integer of 15 to 1860, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:53, and where b is greater than or equal to a + 14.

#### **[0348] FEATURES OF PROTEIN ENCODED BY GENE NO: 44**

[0349] In an alternative reading frame, this gene shares sequence homology with a murine testosterone induced transcript (see, e.g., Geneseq Accession No. 758299 ; all references available through this accession are hereby incorporated by reference herein.). This same region also shares sequence homology with a human cancer

suppressor transfer factor protein (see, e.g., Geneseq Accession No. R86875 ; all references available through this accession are hereby incorporated by reference herein.).

**[0350]** The gene encoding the disclosed cDNA is thought to reside on chromosome 11. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 11.

**[0351]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

KAPYSWLADSWPHPSRSPSAQEPRGSCCPSNPDPDDRYNEAGISLYLAQTA  
RGTAAPGEGPVYSTIDPAGEELQTFHGGFPQHPSGDLGPWSQYAPPEWSQG  
(SEQ ID NO: 357). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0352]** This gene is expressed primarily in various embryonic/fetal tissues, particularly fetal brain tissue.

**[0353]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, congenital birth defects, particularly of the central nervous system, and cancers, such as MEN. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, developing, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene

expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0354]** The tissue distribution in fetal and embryonic tissues indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis, detection, prevention and/or treatment of a variety of cancers, most notably cancers of the central nervous system, such as MEN, as well as the disorders of the central nervous system listed above. Representative uses are described in the “Hyperproliferative Disorders” and “Regeneration” sections below and elsewhere herein. Briefly, the expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that polynucleotides and polypeptides of the invention may play a role in the regulation of cellular division, and may show utility in the detection, treatment, and/or prevention of cancer and other proliferative disorders. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, polynucleotides and polypeptides of the invention may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Expression of polynucleotides and polypeptides corresponding to this gene in a variety of systems indicates that this gene may be a player in the progression of these diseases, and may be a beneficial target for inhibitors as therapeutics. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0355]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:54 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the

general formula of a-b, where a is any integer between 1 to 1649 of SEQ ID NO:54, b is an integer of 15 to 1663, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:54, and where b is greater than or equal to a + 14.

**[0356] FEATURES OF PROTEIN ENCODED BY GENE NO: 45**

**[0357]** The gene encoding the disclosed cDNA is thought to reside on chromosome 1. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 1.

**[0358]** This gene is highly homologous to bovine cytochrome b-5 reductase (see e.g., GENBANK: locus BOVCYB5R, accession M83104; Strittmatter et al., J. Biol. Chem. 267:2519-2523 (1992); the references available through the accession number and the captioned reference are hereby incorporated herein by reference). Based on this homology, it is likely that this gene would have activity similar to NADH-cytochrome b5 reductase.

**[0359]** This gene is expressed primarily in liver and lung tissues.

**[0360]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders of the liver and lung including chronic liver failure, bronchitis, emphysema, and chronic lung failure. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hepatic and pulmonary systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hepatic, pulmonary, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of

one, two, three, four, five or all six of the immunogenic epitopes shown in SEQ ID NO: 162 as residues: Arg-31 to Gln-37, Val-88 to Gly-95, Pro-110 to Gln-120, Gln-151 to Ala-163, Asp-231 to Trp-237, Pro-277 to Lys-287. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0361]** The tissue distribution in liver tissue indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection and treatment of liver disorders and cancers (e.g., hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). Representative uses are described in the “Hyperproliferative Disorders”, “Infectious Disease”, and “Binding Activity” sections below, in Example 11, and 27, and elsewhere herein. Alternatively, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection and treatment of disorders associated with developing lungs, particularly in premature infants where the lungs are the last tissues to develop. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis and intervention of lung tumors, since the gene may be involved in the regulation of cell division, particularly since it is expressed in fetal tissue. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0362]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:55 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the

general formula of a-b, where a is any integer between 1 to 1618 of SEQ ID NO:55, b is an integer of 15 to 1632, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:55, and where b is greater than or equal to a + 14.

**[0363] FEATURES OF PROTEIN ENCODED BY GENE NO: 46**

**[0364]** This gene is expressed primarily in tonsil tissue and neutrophils, and, to a lesser extent, in testes tissue, brain and cerebellum tissues.

**[0365]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders of the tonsils, immune system disorders, reproductive disorders, and neural disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the tonsils, and the immune, reproductive, and neural systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, neural, reproductive, tonsils, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one or both of the immunogenic epitopes shown in SEQ ID NO: 163 as residues: Pro-17 to Glu-26, Asp-60 to Val-72. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0366]** The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of a variety of immune system disorders. Representative uses are described in the “Immune Activity” and “Infectious Disease” sections below, in

Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of polynucleotides and polypeptides corresponding to this gene in tonsils as well as neutrophils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. Polynucleotides and polypeptides corresponding to this gene may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, polynucleotides and polypeptides corresponding to this gene may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the treatment and/or diagnosis of conditions concerning proper testicular function (e.g. endocrine function, sperm maturation), as well as cancer. Therefore, polynucleotides and polypeptides corresponding to this gene would be useful in the treatment of male infertility and/or impotence. Polynucleotides and polypeptides corresponding to this gene is also useful in assays designed to identify binding agents, as such agents (antagonists) would be useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, polynucleotides and polypeptides corresponding to this gene may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. The tissue distribution in brain and cerebellum tissues indicates that polynucleotides and



polypeptides corresponding to this gene would be useful for the detection/treatment of neurodegenerative disease states and behavioural disorders such as Alzheimers Disease, Parkinsons Disease, Huntingtons Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0367]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:56 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2219 of SEQ ID NO:56, b is an integer of 15 to 2233, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:56, and where b is greater than or equal to a + 14.

**[0368] FEATURES OF PROTEIN ENCODED BY GENE NO: 47**

**[0369]** The translation product of this gene shares sequence homology with seven trans-membrane receptors and plectin, which is thought to be important in muscular dystrophy and multiple other diseases.

**[0370]** The gene encoding the disclosed cDNA is thought to reside on chromosome 16. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 16.

**[0371]** This gene is expressed primarily in brain, fetal organs and placental tissue, and, to a lesser extent, in several other organs and tissues.

**[0372]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders of the central nervous system, fetal and developing organs. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, developing and fetal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, developing, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one, two or all three of the immunogenic epitopes shown in SEQ ID NO: 164 as residues: Arg-13 to Trp-19, Leu-76 to Ala-92, Ser-100 to Arg-105. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0373]** The tissue distribution and homology to plectin and seven transmembrane receptors indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the treatment and/or diagnosis of disorders of the central nervous system, as well as developing and fetal systems. Moreover, the expression within fetal tissue indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, cancer, and other proliferative conditions. Representative uses

are described in the “Hyperproliferative Disorders” and “Regeneration” sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain neurodegenerative disorders, such as spinal muscular atrophy (SMA). Because of potential roles in proliferation and differentiation, polynucleotides and polypeptides corresponding to this gene may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention would be useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus, polynucleotides and polypeptides corresponding to this gene may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The polynucleotides and polypeptides corresponding to this gene would be useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[0374] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:57 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention

are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1949 of SEQ ID NO:57, b is an integer of 15 to 1963, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:57, and where b is greater than or equal to a + 14.

**[0375] FEATURES OF PROTEIN ENCODED BY GENE NO: 48**

**[0376]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group:

LQQTMQAMLHFGGRLAQLRGTSKEAASDPSDSPNLPTPGSWW (SEQ ID NO: 358), EQLTQASRVYASGGTEGFPLSRWAPGRHGTAEEGAQERPLPTDE (SEQ ID NO: 359),

MAPGRGLWLGRFLGVPGGPAENENGALKSRRPSSWLPPTVSVLAL (SEQ ID NO: 360), VKRGAPPEMPSPQELEASAPRMVQTHRAVRALCDHTAARPDQLS (SEQ ID NO: 361), FRRGEVLRVITTVDEDWLRCGRDGMGLVPVGYTSLVL (SEQ ID NO: 362), and/or

LQQTMQAMLHFGGRLAQLRGTSKEAASDPSDSPNLPTPGSWWEQLTQASRVYASGGTEGFPLSRWAPGRHGTAEEGAQERPLPTDEMAPGRGLWLGRFLGVPGGPAENENGALKSRRPSSWLPPTVSVLALVKRGAPPEMPSPQELEASAPRMVQTHRAVRALCDHTAARPDQLSFRRGEVLRVITTVDEDWLRCGRDGMGLVPVGYTSLVL (SEQ ID NO: 363). Moreover, fragments and variants of these

polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0377]** A portion of the translation product of this gene shares sequence homology with SH3 domain of human SH3P17 protein (see, e.g., Genseq accession number W34234; all references available through this accession are hereby incorporated by reference herein) which is thought to be important in cell growth, malignancy, and/or

signal transduction processes. Therefore, it is likely that the translation product of this gene shares at least some biological activity with polypeptides/proteins possessing SH domains.

**[0378]** This gene is expressed primarily in synovium, synovial sarcoma, and chondrosarcoma tissues, and, to a lesser extent, in endometrial stromal cells.

**[0379]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, skeletal and reproductive disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skeletal and reproductive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., skeletal, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0380]** The tissue distribution in skeletal tissues indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, diagnosis, prevention and/or treatment of disorders and conditions affecting the skeletal system, in particular osteoporosis as well as disorders afflicting connective tissues (e.g., arthritis, trauma, tendonitis, chondromalacia and inflammation). The polynucleotides and polypeptides of the invention would be useful in the diagnosis or treatment of various autoimmune disorders such as rheumatoid arthritis, lupus, scleroderma, and dermatomyositis as well as dwarfism, spinal deformation, and specific joint abnormalities as well as chondrodysplasias (i.e., spondyloepiphyseal dysplasia congenita, familial arthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Alternatively, the tissue distribution in endometrium indicates that polynucleotides and polypeptides corresponding to this gene would be useful for treating female infertility. The polynucleotides and polypeptides of the invention are

likely involved in preparation of the endometrium of implantation and could be administered either topically or orally. Alternatively, this gene could be transfected in gene-replacement treatments into the cells of the endometrium and the protein products could be produced. Similarly, these treatments could be performed during artificial insemination for the purpose of increasing the likelihood of implantation and development of a healthy embryo. In both cases this gene or its gene product could be administered at later stages of pregnancy to promote healthy development of the endometrium. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0381]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:58 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1253 of SEQ ID NO:58, b is an integer of 15 to 1267, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:58, and where b is greater than or equal to a + 14.

**[0382] FEATURES OF PROTEIN ENCODED BY GENE NO: 49**

**[0383]** The gene encoding the disclosed cDNA is believed to reside on chromosome 7. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 7.

**[0384]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group:

ARACPRXGAAVEKLGGKPVQPSKPTCCSQVKA EGLIFAGLTGLKLLPSSLQ

RAVFVRQCLGFWNDGSRALQ (SEQ ID NO:364) and MSPNLNATHHTSAQTPGFMERKTTHTVAQALSHAVRTIRGARSPLRPDAS RTP TSCQMSTQSLICKARLPSFQNP RHCLTKTALCKELGSNLSPVRPAKISPSALT CEQHVGL ESGWTGFPPSFSTAAPXLGQARA (SEQ ID NO: 365). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0385]** This gene is expressed primarily in hypothalamus, hepatocellular tumor, ovarian cancer reexcision and, to a lesser extent, in other tissues.

**[0386]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, obesity, metabolic disorders, and hepatocellular tumors. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the, endocrine system, hypothalamus and hepatocellular tumor, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hypothalamus, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0387]** The tissue distribution in hypothalamus and hepatocellular tumors indicates that the protein products of this gene would be useful for detection, treatment, and/or prevention of obesity, metabolic disorders, and hepatocellular tumors. Similarly, the tissue distribution indicates that polynucleotides and polypeptides corresponding to

this gene would be useful for the detection, treatment, and/or prevention of various endocrine disorders and cancers, particularly Addison's disease, Cushing's Syndrome, and disorders and/or cancers of the pancreas (e.g., diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g., hyper-, hypothyroidism), parathyroid (e.g., hyper-, hypoparathyroidism), hypothalamus, and testes. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0388]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:59 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1281 of SEQ ID NO:59, b is an integer of 15 to 1295, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:59, and where b is greater than or equal to a + 14.

**[0389] FEATURES OF PROTEIN ENCODED BY GENE NO: 50**

**[0390]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:  
 FQSVYHMKLQSSNLPASVYGNNLNCINSSSS (SEQ ID NO: 366). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of



the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

[0391] This gene is expressed primarily in brain, placenta, immune cells (e.g., B-cells and macrophage), fetal tissue and breast.

[0392] Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive, neurological and behavioural disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the CNS, immune and female reproductive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, reproductive, CNS, cancerous and wounded tissues) or bodily fluids (e.g., lymph, breast milk, amniotic fluid, serum, plasma, urine, synovial fluid or cerebrospinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

[0393] The tissue distribution in brain indicates the protein product of this clone would be useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of Polynucleotides and polypeptides

corresponding to this gene in regions of the brain indicates it plays a role in normal neural function. Potentially, polynucleotides and polypeptides corresponding to this gene would be involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. The tissue distribution in B-cells and macrophage indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. Involvement in the regulation of cytokine production, antigen presentation, or other processes indicates a usefulness for treatment of cancer (e.g., by boosting immune responses). Expression in cells of lymphoid origin, indicates the natural gene product would be involved in immune functions. Therefore it would also be useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, polynucleotides and polypeptides corresponding to this gene is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. In addition, expression in breast and placenta indicates a role in the detection and/or treatment of female infertility and/or pregnancy disorders. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Moreover, the expression

within fetal tissue and other cellular sources marked by proliferating cells indicates this protein may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain degenerative disorders, such as spinal muscular atrophy (SMA). Alternatively, polynucleotides and polypeptides corresponding to this gene may be involved in the pattern of cellular proliferation that accompanies early embryogenesis. Thus, aberrant expression of polynucleotides and polypeptides corresponding to this gene in tissues - particularly adult tissues - may correlate with patterns of abnormal cellular proliferation, such as found in various cancers. Because of potential roles in proliferation and differentiation, polynucleotides and polypeptides corresponding to this gene may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention would be useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus this protein may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. The protein would be useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as,

antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0394]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:60 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 901 of SEQ ID NO:60, b is an integer of 15 to 915, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:60, and where b is greater than or equal to a + 14.

**[0395] FEATURES OF PROTEIN ENCODED BY GENE NO: 51**

**[0396]** This gene is expressed primarily in adipocytes.

**[0397]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, obesity, Nasu-Hakola disease, cardiovascular disease, non-insulin-dependent diabetes mellitus. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the adipose, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., endocrine, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one or both of the immunogenic epitopes shown in SEQ ID

NO: 168 as residues: Asp-6 to Arg-12, Lys-31 to Leu-41. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0398]** The tissue distribution in adipose tissue indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the treatment and diagnosis of endocrine and metabolic disorders related to lipids and adipose tissue, such as obesity, Nasu-Hakola disease (membranous lipodystrophy), cardiovascular disease, lipidemia, non-insulin-dependent diabetes mellitus, stroke and carcinoma. Furthermore, polynucleotides and polypeptides corresponding to this gene may show utility in ameliorating conditions which occur secondary to aberrant fatty-acid metabolism (e.g., aberrant myelin sheath development), either directly or indirectly. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0399]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:61 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1431 of SEQ ID NO:61, b is an integer of 15 to 1445, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:61, and where b is greater than or equal to a + 14.

#### **[0400] FEATURES OF PROTEIN ENCODED BY GENE NO: 52**

[0401] The gene encoding the disclosed cDNA is thought to reside on chromosome 1. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 1.

[0402] In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence: GLSIHDGTWKSAI YGFGDQSNLRKLRNVSNLKPVPLIGPKLKRRWPISYCRELKGYSIPFMGSDVS VVRRTQRYLYENLEESPVQYAAAYVTVGGITSVIKLMFAGLFFLFFVRFGIGRQ LLIKFPWFSSFGYFSKQGPTQKQIDAASFTLTFFGQGYSQGTGTDKNKPNIKIC TQVKGP EAGYVATPIAMVQAAMTLLSDASHLPKAGGVFTPGA AFSKTKLI DRLNKHGIEFSVISSEV (SEQ ID NO: 367) Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

[0403] This gene is expressed primarily in testes, endometrial tumor tissue, prostate cancer tissue, immune tissue (e.g., bone marrow and T-cells) and placenta tissue, and, to a lesser extent, in several other tissues and organs.

[0404] Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive diseases and disorders, cancers and hematopoietic disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hematopoietic and reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene

expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one or both of the immunogenic epitopes shown in SEQ ID NO: 169 as residues: Phe-32 to Gln-41, Gln-54 to Asn-68. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0405]** The tissue distribution in testes tissue and bone marrow indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the treatment and/or diagnosis of disorders of the hematopoietic and reproductive systems, and cancers thereof. The tissue distribution in bone marrow and T-cells indicates the protein product of this clone would be useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. Involvement in the regulation of cytokine production, antigen presentation, or other processes indicates a usefulness for treatment of cancer (e.g. by boosting immune responses). Expression in cells of lymphoid origin, indicates the natural gene product would be involved in immune functions. Therefore it would also be useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, polynucleotides and polypeptides corresponding to this gene is thought to be useful in the expansion of stem cells and

committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the treatment and diagnosis of conditions concerning proper testicular function (e.g., endocrine function, sperm maturation), as well as cancer. Therefore, polynucleotides and polypeptides corresponding to this gene would be useful in the treatment of male infertility and/or impotence. Polynucleotides and polypeptides corresponding to this gene is also useful in assays designed to identify binding agents, as such agents (antagonists) would be useful as male contraceptive agents. Similarly, the protein is believed to be useful in the treatment and/or diagnosis of testicular cancer. The testes are also a site of active gene expression of transcripts that may be expressed, particularly at low levels, in other tissues of the body. Therefore, polynucleotides and polypeptides corresponding to this gene may be expressed in other specific tissues or organs where it may play related functional roles in other processes, such as hematopoiesis, inflammation, bone formation, and kidney function, to name a few possible target indications. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0406]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:62 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1086 of SEQ ID NO:62, b is an integer of 15 to 1100, where both a and b correspond to the positions of



nucleotide residues shown in SEQ ID NO:62, and where b is greater than or equal to a + 14.

**[0407] FEATURES OF PROTEIN ENCODED BY GENE NO: 53**

**[0408]** The translation product of this gene has homology with metallothioneine proteins from several organisms.

**[0409]** This gene is expressed primarily in ovarian cancer, fetal tissue (e.g., liver, spleen, and heart), testes, embryo, colon, T-cells, neutrophils, tonsils, B-cell lymphoma, and to a lesser extent in many other tissues.

**[0410]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, reproductive defects, and lymphoid and ovarian cancers. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and female reproductive systems, and of lymphoid and ovarian cancers, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of the immunogenic epitopes shown in SEQ ID NO: 170 as residues: Leu-39 to Ser-47. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0411]** The tissue distribution in ovarian cancer, tonsils, and B-cell lymphoma indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the study, detection and/or treatment of female reproductive disorders, gonadal and general lymphoid neoplasias, and cancers thereof. The tissue distribution

in immune cells (e.g., neutrophils and T-cells) indicates the protein product of this clone would be useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. Involvement in the regulation of cytokine production, antigen presentation, or other processes indicates a usefulness for treatment of cancer (e.g. by boosting immune responses). Expression in cells of lymphoid origin, indicates the natural gene product would be involved in immune functions. Therefore it would also be useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, polynucleotides and polypeptides corresponding to this gene is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Expression of polynucleotides and polypeptides corresponding to this gene in tonsils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells.

Polynucleotides and polypeptides corresponding to this gene may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor

marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, polynucleotides and polypeptides corresponding to this gene may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0412]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:63 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1485 of SEQ ID NO:63, b is an integer of 15 to 1499, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:63, and where b is greater than or equal to a + 14.

**[0413] FEATURES OF PROTEIN ENCODED BY GENE NO: 54**

**[0414]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group:

MDPDRAFIGESRQFAQCLIFGFLFLTSGMLISVLGIWVPGCGSNWAQEPLNE  
TDTGDSEPRMCGFLSLQIMGPLIVLVGLCFFVVAHVKKRNTLNAGQDASERE  
EGQIQIMEPVQVTVGDSVIIFPPPPPPYFPSSASAVAESPGTNSLLPNENPPSY  
YSIFNYGTPTSEGAASERDCESIYTISGTNSSSEASHTPHLPSELPPRYEEKENA

AATFLPLSSEPSPP (SEQ ID NO: 369), and/or  
MDPDRAFIGGESRQFAQCLIFGFLFLTSGMLISVLGIWVPGCGSNWAQEPLNE  
TDTGDSEPR (SEQ ID NO: 368). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

[0415] This gene is expressed primarily in adult kidney and pulmonary tissues, as well as in osteoblasts.

[0416] Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, metabolic, endocrine and skeletal disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine, skeletal, metabolic and developmental systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., endocrine, skeletal, cancerous and wounded tissues) or bodily fluids (e.g., sputum, lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one, two, three, four, five or all six of the immunogenic epitopes shown in SEQ ID NO: 171 as residues: Ala-35 to Gly-45, Pro-67 to Pro-73, Pro-91 to Ser-97, Thr-127 to Leu-139, Leu-143 to Asn-152, Ser-162 to Pro-167. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0417]** The tissue distribution in kidney tissue and osteoblasts indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the study, diagnosis and/or treatment of various endocrine and skeletal disorders. Furthermore, elevated levels of expression of polynucleotides and polypeptides corresponding to this gene in osteoblasts indicates that it may play a role in the survival, proliferation, and/or growth of osteoblasts. Therefore, it may be useful in influencing bone mass in such conditions as osteoporosis. Alternatively, the tissue distribution in kidney indicates that this gene or gene product would be useful in the treatment and/or detection of kidney diseases including renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilm's Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0418]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:64 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 641 of SEQ ID NO:64, b is an integer of 15 to 655, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:64, and where b is greater than or equal to a + 14.

**[0419] FEATURES OF PROTEIN ENCODED BY GENE NO: 55**

**[0420]** This gene is expressed primarily in neutrophils and embryonic tissues.

**[0421]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune system disorders and cancers, and developmental disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and developing systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, developing, cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one, two, three, four, five, six, seven or all eight of the immunogenic epitopes shown in SEQ ID NO: 172 as residues: Gln-21 to Ala-33, Lys-48 to Leu-54, His-91 to Arg-97, Ala-143 to Gln-148, Glu-173 to Thr-179, Ser-215 to Lys-254, Arg-262 to Glu-269, Ala-309 to Gly-314. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0422]** The tissue distribution in neutrophils and embryonic tissues indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis, study and/or treatment of various developmental and immune system disorders and cancers thereof, as well as cancers of other tissues where expression of this gene has been observed. Furthermore, expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that this protein may play a role in the regulation of cellular division, and may show utility in the detection, treatment, and/or prevention of cancer and other proliferative disorders. Similarly, embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus, this protein may also be involved in apoptosis or

tissue differentiation and could again be useful in cancer therapy. Alternatively, expression of polynucleotides and polypeptides corresponding to this gene in neutrophils also strongly indicates a role for this protein in immune function and immune surveillance. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0423]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:65 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1436 of SEQ ID NO:65, b is an integer of 15 to 1450, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:65, and where b is greater than or equal to a + 14.

**[0424] FEATURES OF PROTEIN ENCODED BY GENE NO: 56**

**[0425]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

FDFIASLLKANRLSLQTCELLLAAALLPSERYKAISI (SEQ ID NO: 370).

Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind

polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0426]** This gene is expressed primarily in fetal liver, spleen and, to a lesser extent, in breast.

**[0427]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and haemopoietic diseases and/or disorders, in addition to, fetal development. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the circulatory system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hematopoietic, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one or both of the immunogenic epitopes shown in SEQ ID NO: 173 as residues: Ile-50 to Ser-61, Pro-75 to Ser-104. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0428]** The tissue distribution in fetal liver and spleen indicates that polynucleotides and polypeptides corresponding to this gene would be useful for detection, treatment, and/or prevention of haemopoietic disorders involving stem cell production and maturation. Similarly, polynucleotides and polypeptides corresponding to this gene would be useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein.



Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, polynucleotides and polypeptides corresponding to this gene may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0429]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:66 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 656 of SEQ ID NO:66, b is an integer of 15 to 670, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:66, and where b is greater than or equal to a + 14.

**[0430] FEATURES OF PROTEIN ENCODED BY GENE NO: 57**

**[0431]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

MNKKAEKPSALPGWANVWKLMLVTVCASLIITSDSVVSTVRLKGSCEDY  
LGLSCGNTSHAY (SEQ ID NO: 371). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at

least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0432]** This gene is expressed primarily in adult pulmonary cells.

**[0433]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, emphysema and other pulmonary diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the pulmonary system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., lung, cardiovascular, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, sputum, pulmonary surfactant, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0434]** The tissue distribution in adult pulmonary cells indicates that polynucleotides and polypeptides corresponding to this gene would be useful for detection, treatment, and/or prevention of disorders of the pulmonary systems, especially emphysema, asthma, and other similar dysfunctions. Representative uses are described elsewhere herein. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0435]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:67 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1678 of SEQ ID NO:67, b is an integer of 15 to 1692, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:67, and where b is greater than or equal to a + 14.

**[0436] FEATURES OF PROTEIN ENCODED BY GENE NO: 58**

**[0437]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

MSADGAEADGSTQVTVEEPVQQPSVVDRAVSMPLISSTCDMVSAAYASTKE  
 SYPHVKTVCDAAEKGVRTLTAADVSGAQPILSKLEPQIASASEYAHRLDKL  
 EENLPILQQPTEKVLADTKELVSSKVSGAQEMVSSAKDTVATQLSEAVDATR  
 GAVQSGVDKTKSVVTGGVQSVMGSRGQMVLSGVDTVLGKSEEWADNHL  
 LTDAELARIATSLDGFDAVSVQQQRQEQSYFVRLGSLSERLRQHAYEHS  
 LGLKLRATKQRAQEALLQLSQALSLMETVKQGVQKLVEGQEKHLHQM  
 WLSWNQKQLQGPEKEPPKPEQVESRALTMFRDIAQQLQATCTSLGSSIQ  
 GLPTNVKDQVQQARRQVEDLQATFSSIHQFQDLSSILAQSRERVASAREALD  
 HMVEYVAQNTPVTWLVGPFAPGITEKAPEEKK (SEQ ID NO: 372) which  
 shares homology with a human adipocyte differentiation-related  
 protein (see GenBank Accession CAA65989 and Heid, H.W., et al.,  
 Biochem. J. 320, 1025-1030 (1996); all references available  
 through this accession and citation are hereby incorporated herein  
 by reference). Moreover, fragments and variants of these  
 polypeptides (such as, for example, fragments as described  
 herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%,  
 98%, 99%, or 100% identical to these polypeptides, or  
 polypeptides encoded by a polynucleotide which hybridizes,  
 under stringent conditions, to the polynucleotide encoding  
 these polypeptides) are encompassed by the invention. Antibodies  
 that bind polypeptides of the invention and polynucleotides  
 encoding

these polypeptides are also encompassed by the invention. This gene is expressed primarily in hypothalamus (schizophrenic), and, to a lesser extent, in cerebellum.

**[0438]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, schizophrenia and hypothalamic diseases and/or diseases. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., CNS, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0439]** The tissue distribution in hypothalamus (schizophrenic) and, to a lesser extent, in cerebellum indicates that polynucleotides and polypeptides corresponding to this gene would be useful for detection, treatment, and/or prevention of neurological disorders, especially schizophrenia, neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, polynucleotides and polypeptides corresponding

to this gene are involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0440]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:68 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 641 of SEQ ID NO:68, b is an integer of 15 to 655, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:68, and where b is greater than or equal to a + 14.

**[0441] FEATURES OF PROTEIN ENCODED BY GENE NO: 5**

**[0442]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

MLCKSLLYCVVSYLYYFVFIYFFPVFLICSWLELQMWNLQIGRADCFQNTLV  
YVLSLCLQYKNHPA (SEQ ID NO: 373). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0443]** This gene is expressed primarily in CD34 positive hematopoietic cells.

**[0444]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic diseases and/or disorders; impaired immune function; susceptibility to infections; lymphomas and leukemias. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hematopoietic, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0445]** The tissue distribution in CD34 positive cells indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis, detection, prevention and/or treatment of a variety of hematopoietic disorders. Expression of this gene product particularly in CD34 positive cells indicates that polynucleotides and polypeptides of the invention may play a role in the proliferation; survival; differentiation; and/or activation of early stem and committed progenitor cells within the hematopoietic system. Thus, polynucleotides and polypeptides of the invention may be useful in determining the numbers and proportions of different hematopoietic cell lineages both in vitro and in vivo. Additionally, the tissue distribution indicates polynucleotides and polypeptides corresponding to this gene would be useful for the treatment and diagnosis of hematopoietic related disorders such as anemia, pancytopenia, leukopenia, thrombocytopenia or leukemia since stromal cells are important in the production of cells of hematopoietic lineages. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the uses include bone marrow cell ex-vivo culture, bone marrow transplantation, bone marrow reconstitution, radiotherapy or chemotherapy of

neoplasia. The gene product may also be involved in lymphopoiesis, therefore, it can be used in immune disorders such as infection, inflammation, allergy, immunodeficiency etc. In addition, polynucleotides and polypeptides of the invention may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0446]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:69 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1604 of SEQ ID NO:69, b is an integer of 15 to 1618, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:69, and where b is greater than or equal to a + 14.

**[0447] FEATURES OF PROTEIN ENCODED BY GENE NO: 60**

**[0448]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group: IDLSFPSTNVSLDRNTTKPSVNVG (SEQ ID NO: 374), VAHACNPSTLGG (SEQ ID NO: 375), GGQITRSGDQDQPDQHG (SEQ ID NO: 376), GFTMLVRLVLIS (SEQ ID NO: 377), and PRDLPTSASQSAGITGMSHPARPKLLFN (SEQ ID NO: 378). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%,

or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0449]** This gene is expressed primarily in dermatofibrosarcoma protuberance and 12 week old early human embryos.

**[0450]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, dermatofibrosarcoma; cancer; abnormal cell proliferation; embryological/developmental defects; inhibition of apoptosis; and hematopoietic diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skin and epithelium, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., integumentary, reproductive, developmental, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, amniotic fluid, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0451]** The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis and/or treatment of abnormal cellular proliferation, such as cancer. Expression of this gene in dermatofibrosarcoma and 12 week early stage embryos indicates that polynucleotides and polypeptides of the invention are involved in cellular proliferation and/or a block in differentiation. Polynucleotides and polypeptides of the invention may drive cellular proliferation directly, or may play a role in inhibiting apoptosis or interfering with differentiation events. Similarly, polynucleotides and polypeptides of the invention would be useful for the treatment, diagnosis, and/or prevention of various



skin disorders. Representative uses are described in the "Biological Activity", "Hyperproliferative Disorders", "Infectious Disease", and "Regeneration" sections below, in Example 11, 19, and 20, and elsewhere herein. Briefly, the protein would be useful in detecting, treating, and/or preventing congenital disorders (i.e. nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (i.e., keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (i.e., wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (i.e., lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. In addition, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (i.e., cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athlete's foot, and ringworm). Moreover, polynucleotides and polypeptides corresponding to this gene may also be useful for the treatment or diagnosis of various connective tissue disorders (i.e., arthritis, trauma, tendonitis, chondromalacia and inflammation, etc.), autoimmune disorders (i.e., rheumatoid arthritis, lupus, scleroderma, dermatomyositis, etc.), dwarfism, spinal deformation, joint abnormalities, and chondrodysplasias (i.e., spondyloepiphyseal dysplasia congenita, familial osteoarthritis, Atelosteogenesis type II, metaphyseal chondrodysplasia type Schmid). Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0452]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:70 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically

excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1788 of SEQ ID NO:70, b is an integer of 15 to 1802, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:70, and where b is greater than or equal to a + 14.

**[0453] FEATURES OF PROTEIN ENCODED BY GENE NO: 61**

**[0454]** This gene is expressed primarily in neutrophils.

**[0455]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders affecting the immune system. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue from an individual not having the disorder.

**[0456]** The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis, detection, prevention and/or treatment of immune system disorders, especially those affecting neutrophils. Representative uses are described in the “Immune Activity” and “Infectious Disease” sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, this gene product may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the

gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore it may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0457]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:71 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1278 of SEQ ID NO:71, b is an integer of 15 to 1292, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:71, and where b is greater than or equal to a + 14.

**[0458] FEATURES OF PROTEIN ENCODED BY GENE NO: 62**

**[0459]** The translation product of this gene shares sequence homology with angiotensin II receptor which is thought to be important in ligand binding for blood pressure regulation. (see, e.g., GenBank Accession No. gi|387891, gi|1763532, and/or gi|349736; all references available through these accessions are hereby incorporated herein by reference). In specific embodiments, polypeptides of the invention

comprise, or alternatively consist of, the following amino acid sequence (portion of extracellular domain):

PFWAAESALDFHWPFGGALCKMVLTA TVLNVYASIFLITALSVARY (SEQ ID NO: 379). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

[0460] This gene is expressed primarily in 7TM-pbfd and PCMIX libraries (tissue types unknown).

[0461] Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, blood pressure regulatory diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the vascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of the immunogenic epitopes shown in SEQ ID NO: 179 as residues: Gln-117 to Ser-126. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

[0462] The tissue distribution and homology to angiotensin II receptor indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the

study, detection, treatment, and/or prevention of vascular diseases such as blood pressure regulatory disorders. Representative uses are described elsewhere herein. In particular, the extracellular region of the receptor can be used as a soluble antagonist. Moreover, polynucleotides and polypeptides of the invention would be useful in the detection, treatment, and/or prevention of a variety of vascular disorders and conditions, which include, but are not limited to microvascular disease, vascular leak syndrome, aneurysm, stroke, embolism, thrombosis, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0463]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:72 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 869 of SEQ ID NO:72, b is an integer of 15 to 883, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:72, and where b is greater than or equal to a + 14.

**[0464] FEATURES OF PROTEIN ENCODED BY GENE NO: 63**

**[0465]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group: THADKNQVRNSN (SEQ ID NO: 380), QFLSWEQCTGNTESQ (SEQ ID NO: 381), VRRPKAKGXQTSN (SEQ ID NO: 382), PTQLNKHKPTTKERRRKGL (SEQ ID NO: 383), and/or LISKHENIY (SEQ ID NO: 384). Moreover, fragments and

variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0466]** This gene is expressed primarily in neutrophils.

**[0467]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders affecting the immune system. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0468]** The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis and/or treatment of immune system disorders, especially those affecting neutrophils. Representative uses are described in the “Immune Activity” and “Infectious Disease” sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, polynucleotides and polypeptides of the invention may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore

polynucleotides and polypeptides of the invention may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, polynucleotides and polypeptides of the invention may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0469]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:73 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 771 of SEQ ID NO:73, b is an integer of 15 to 785, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:73, and where b is greater than or equal to a + 14.

**[0470] FEATURES OF PROTEIN ENCODED BY GENE NO: 64**

**[0471]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

TLYIXXMXTQTWRDQGRCGRDXINCIV (SEQ ID NO: 385). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these

polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0472]** This gene is expressed primarily in brain tissue from a manic depressive, in some cancer tissues such as ovarian cancer, and in spleen from a patient with chronic lymphocytic leukemia and, to a lesser extent, in other tissues.

**[0473]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, brain disorders (e.g., manic depression), and tumorigenesis. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system (CNS), reproductive system, and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., brain, reproductive, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one or both of the immunogenic epitopes shown in SEQ ID NO: 181 as residues: Thr-29 to Ala-37, Arg-41 to Lys-46. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0474]** The tissue distribution primarily in brain tissue from a manic depressive indicates that polynucleotides and polypeptides corresponding to this gene would be useful for diagnosing and treating manic depression and tumorigenesis. The tissue distribution in brain also indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and



"Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that polynucleotides and polypeptides corresponding to this gene may play a role in normal neural function. Potentially, polynucleotides and polypeptides corresponding to this gene are involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[0475] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:74 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2327 of SEQ ID NO:74, b is an integer of 15 to 2341, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:74, and where b is greater than or equal to a + 14.

**[0476] FEATURES OF PROTEIN ENCODED BY GENE NO: 65**

**[0477]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

SLCTPGRGWEESWGSSLPNLTGWSVSSLDNNDV (SEQ ID NO: 386). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0478]** This gene is expressed primarily in metastatic melanoma spleen, rhabdomyosarcoma, and IL-1 induced neutrophils and, to a lesser extent, in other tissues.

**[0479]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, tumorigenesis, metastasis and inflammatory disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the skin, connective tissue and immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., skin, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0480]** The tissue distribution in metastatic melanoma spleen, rhabdomyosarcoma, and IL-1 induced neutrophils indicates that polynucleotides and polypeptides corresponding to this gene would be useful for detection, treatment, and/or prevention of certain tumors such as melanoma, rhabdomyosarcoma and inflammatory disorders.

Similarly, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the treatment, diagnosis, and/or prevention of various skin disorders including congenital disorders (e.g., nevi, moles, freckles, Mongolian spots, hemangiomas, port-wine syndrome), integumentary tumors (e.g., keratoses, Bowen's disease, basal cell carcinoma, squamous cell carcinoma, malignant melanoma, Paget's disease, mycosis fungoides, and Kaposi's sarcoma), injuries and inflammation of the skin (e.g., wounds, rashes, prickly heat disorder, psoriasis, dermatitis), atherosclerosis, urticaria, eczema, photosensitivity, autoimmune disorders (e.g., lupus erythematosus, vitiligo, dermatomyositis, morphea, scleroderma, pemphigoid, and pemphigus), keloids, striae, erythema, petechiae, purpura, and xanthelasma. Moreover, such disorders may predispose increased susceptibility to viral and bacterial infections of the skin (e.g., cold sores, warts, chickenpox, molluscum contagiosum, herpes zoster, boils, cellulitis, erysipelas, impetigo, tinea, athlete's foot, and ringworm). The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. Involvement in the regulation of cytokine production, antigen presentation, or other processes indicates a usefulness for treatment of cancer (e.g., by boosting immune responses). Expression in cells of lymphoid origin, indicates the natural gene product would be involved in immune functions. Therefore polynucleotides and polypeptides of the invention would also be useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus

erythematosis, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0481]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:75 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1868 of SEQ ID NO:75, b is an integer of 15 to 1882, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:75, and where b is greater than or equal to a + 14.

**[0482] FEATURES OF PROTEIN ENCODED BY GENE NO: 66**

**[0483]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group:

DSESSSEEEFEGVVGNRSRFAKGDYLRCKICYPLCGFVILAACVVACVGLV  
WMQVALKEDLDALKEKFRTMESNQKSSFQEIPKLNEELLSKQKQLEKIESGE  
MGLNKVWINITEMNKQISLLTSAVNHLKANVKSAADLISLPTTVEGLQKSVA  
SIGXTLNSVHLAVEALQKTVDEHKKTMEQLQSDMNQHFLKETPGSNQIIPSPS  
ATSELDNKTHSENKQMGDRSATLKRQSLDQVTNRDTVKIQSIKKEG (SEQ

ID NO:393),

MQVALKEDLDALKEKFRTMESNQKSSFQEIPKLNEELLSKQKQLEKIESGEM  
GLNKVWINITEMNKQISLLTSAVNHLKANVKSAA DLISLPTTVEGLQKSVASI  
GXTLNSVHLAVEALQKTVDEHKKTMELLQSDMNQHFLKETPGSNQIIPSPA  
TSELDNKTHSENKQMGDRSATLKRQSLDQVTNRTDTVKIQSIKKEG (SEQ  
ID NO:387), MQVALKEDLDALKEKFRTMESNQKSSFQEIPKLNEELLSKQKQ  
(SEQ ID NO:388),

LEKIESGEMGLNKVWINITEMNKQISLLTSAVNHLKANVKSAA (SEQ ID  
NO:389), DLISLPTTVEGLQKSVASIGXTLNSVHLAVEALQKTVDEHKKT (SEQ  
ID NO:390), MELLQSDMNQHFLKETPGSNQIIPSPSATSELDNKTHSENKQ  
(SEQ ID NO:391), and/or MGDRSATLKRQSLDQVTNRTDTVKIQSIKKEG (SEQ  
ID NO: 392). Moreover, fragments and variants of these polypeptides (such as, for  
example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%,  
96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides  
encoded by a polynucleotide which hybridizes, under stringent conditions, to the  
polynucleotide encoding these polypeptides) are encompassed by the invention.  
Antibodies that bind polypeptides of the invention and polynucleotides encoding  
these polypeptides are also encompassed by the invention.

[0484] The gene encoding the disclosed cDNA is believed to reside on chromosome  
1. Accordingly, polynucleotides related to this invention would be useful as a marker  
in linkage analysis for chromosome 1.

[0485] This gene is expressed primarily in fetal, placental and infant brain tissues,  
and, to a lesser extent, in many normal and neoplastic cell types.

[0486] Polynucleotides and polypeptides of the invention would be useful as reagents  
for differential identification of the tissue(s) or cell type(s) present in a biological  
sample and for diagnosis of diseases and conditions which include, but are not limited  
to, developmental disorders, cancer and general growth disorders. Similarly,  
polypeptides and antibodies directed to these polypeptides would be useful in  
providing immunological probes for differential identification of the tissue(s) or cell  
type(s). For a number of disorders of the above tissues or cells, particularly of the  
reproductive, developing, and nervous systems, expression of this gene at

significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, developmental, neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of the immunogenic epitopes shown in SEQ ID NO: 183 as residues: Cys-30 to Asn-44. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

[0487] The tissue distribution in infant brain and embryonic tissues indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the study, detection and/or treatment of growth and neoplastic disorders. Furthermore, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of cancer and other proliferative disorders. Expression within embryonic tissue and other cellular sources marked by proliferating cells indicates that polynucleotides and polypeptides of the invention may play a role in the regulation of cellular division. Embryonic development also involves decisions involving cell differentiation and/or apoptosis in pattern formation. Thus polynucleotides and polypeptides of the invention may also be involved in apoptosis or tissue differentiation and could again be useful in cancer therapy. Alternatively, the tissue distribution in brain indicates polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia,

mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, polynucleotides and polypeptides of the invention are involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0488]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:76 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2878 of SEQ ID NO:76, b is an integer of 15 to 2892, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:76, and where b is greater than or equal to a + 14.

**[0489] FEATURES OF PROTEIN ENCODED BY GENE NO: 67**

**[0490]** This gene is apparently exclusively in fetal heart tissue.

**[0491]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited

to, cardiovascular and growth defects. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the developing cardiovascular system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., cardiovascular, heart, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0492]** The tissue distribution in fetal heart tissue indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the study, detection and/or treatment of disorders and growth defects of heart development and function. Furthermore, the tissue distribution in fetal heart tissue indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of conditions and pathologies of the cardiovascular system, such as heart disease, restenosis, atherosclerosis, stroke, angina, thrombosis, and wound healing. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0493]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:77 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1659 of SEQ ID NO:77, b is an integer of 15 to 1673, where both a and b correspond to the positions of



nucleotide residues shown in SEQ ID NO:77, and where b is greater than or equal to a + 14.

**[0494] FEATURES OF PROTEIN ENCODED BY GENE NO: 68**

**[0495]** This gene is expressed primarily in pancreas islet cell tumor tissue.

**[0496]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, digestive and metabolic defects and tumors, particularly tumors of the pancreas. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the endocrine system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., endocrine, pancreas, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0497]** The tissue distribution in pancreas islet cell tumor tissue indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the study, detection and/or treatment of hormonal and neoplastic disorders of endocrine organs and metabolism. Additionally, the tissue distribution indicates polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of various endocrine disorders and cancers.

Representative uses are described in the "Biological Activity", "Hyperproliferative Disorders", and "Binding Activity" sections below, in Example 11, 17, 18, 19, 20 and 27, and elsewhere herein. Briefly, the protein can be used for the detection, treatment, and/or prevention of the Addison's disease, Cushing's Syndrome, and disorders and/or cancers of the pancreas (e.g., diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g., hyper-, hypothyroidism),

parathyroid (e.g., hyper-,hypoparathyroidism), hypothalamus, and testes.

Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0498]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:78 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1447 of SEQ ID NO:78, b is an integer of 15 to 1461, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:78, and where b is greater than or equal to a + 14.

**[0499] FEATURES OF PROTEIN ENCODED BY GENE NO: 69**

**[0500]** This gene is expressed primarily in tonsils.

**[0501]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders of the tonsils, and disorders of the immune system.

Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the tonsils, and the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., tonsils, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken

from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0502]** The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of a variety of immune system disorders. Expression of this gene product in tonsils indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. Representative uses are described in the “Immune Activity” and “Infectious Disease” sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, polynucleotides and polypeptides of the invention may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore polynucleotides and polypeptides of the invention may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, polynucleotides and polypeptides of the invention may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0503]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:79 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1503 of SEQ ID NO:79, b is an integer of 15 to 1517, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:79, and where b is greater than or equal to a + 14.

**[0504] FEATURES OF PROTEIN ENCODED BY GENE NO: 70**

**[0505]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence: SPQFLSSKSLPT (SEQ ID NO:394). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0506]** This gene is expressed primarily in infant brain and spinal cord.

**[0507]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, congenital brain disorders, including various forms of mental retardation, spina bifida, epilepsy, and various mood disorders, including bipolar and unipolar depression. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., brain, CNS, cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic

fluid, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one or both of the immunogenic epitopes shown in SEQ ID NO: 187 as residues: Pro-42 to Lys-49, Lys-56 to Lys-71. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

[0508] The tissue distribution in infant brain and spinal cord indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis, detection, prevention and/or treatment of disorders of the brain and nervous system, including congenital brain disorders, including various forms of mental retardation, spina bifida, epilepsy, and various mood disorders, including bipolar and unipolar depression. Additionally, polynucleotides and polypeptides corresponding to this gene may have cytostatic, thrombotic and/or osteopathic activity. It may also be useful in the treatment of such neurodegenerative disorders as schizophrenia; ALS; or Alzheimer's. The tissue distribution in brain further indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates that polynucleotides and polypeptides corresponding to this gene may play a role in normal neural

function. Potentially, polynucleotides and polypeptides corresponding to this gene are involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0509]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:80 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 560 of SEQ ID NO:80, b is an integer of 15 to 574, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:80, and where b is greater than or equal to a + 14.

**[0510] FEATURES OF PROTEIN ENCODED BY GENE NO: 71**

**[0511]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group:

GPPSPRGLPSLPLHLPAPRRYLQSRYSQSSVSAAARRWGSGWMAWDPWN  
QASGRYARITLLSVQACHQ

PTVWPRAGHSLPERYSLHPHNGDSTHLSGLLTVKCGA (SEQ ID NO: 395),

GPPSPRGLPSLPLHLPAPRRYLQSRYSQSSVSAAA (SEQ ID NO:396),

RRWGSGWMAWDPWNQASGRYARITLLSVQACHQ (SEQ ID NO:397),

GPPSPRGLPSLPLHLPAPRRYLQSRYSQSSVSAAARRWGSGWMAWDPWN  
QASGRYARITLLSVQACHQPTVWPRAGHSLPERYSLHPHNGDSTHLSGLLTV  
KCGAMAGFASYPWSDFPWCWVVCFSFXFFLRQSESLSQKKRQVADELXFG

QSKRDS DGGWMLRSSAGNS (SEQ ID NO:399),  
MESCSVVQAGVKWCDLGSLQPPPRFKQFSWEVEVAVSRDHTIALQXGGQSK  
XLSQKKEKKYVLNATFLNFYFCRDKVLLCCPGWSHIVGLKQSSHLGLRK CW  
DYRHG PLXLALCHFVCK (SEQ ID NO:400), and/or  
PTVWPRAGHSLPERYSLHPHNGDSTHLSGLLTVKCGA (SEQ ID NO:392).

Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0512]** This gene is expressed primarily in neutrophils.

**[0513]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, infection, inflammation and other immune reactions or disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0514]** The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene would be useful for detection, treatment, and/or prevention of immune disorders, such as infection, inflammation, allergy and immunodeficiency. Therefore, polynucleotides and polypeptides corresponding to this gene may have clinical relevance in the treatment of impaired immunity, in the

correction of autoimmunity, in immune modulation, in the treatment of allergy, and in the regulation of inflammation. It may also play a role in influencing differentiation of specific hematopoietic lineages, and may even affect the hematopoietic stem cell. The tissue distribution in neutrophils also indicates that polynucleotides and polypeptides corresponding to this gene may be useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. Involvement in the regulation of cytokine production, antigen presentation, or other processes indicates a usefulness for treatment of cancer (e.g., by boosting immune responses). Expression in cells of lymphoid origin, indicates the natural gene product would be involved in immune functions. Therefore polynucleotides and polypeptides corresponding to this gene would also be useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the



protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0515]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:81 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1441 of SEQ ID NO:81, b is an integer of 15 to 1455, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:81, and where b is greater than or equal to a + 14.

**[0516] FEATURES OF PROTEIN ENCODED BY GENE NO: 72**

**[0517]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence: NQENSLQTN SYLDSTESK (SEQ ID NO: 401). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0518]** The polypeptide of this gene has been determined to have a transmembrane domain at about amino acid position 12 to about 28 of the amino acid sequence referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing about amino acids 29 to about 70 of this protein has also been determined. Based upon these characteristics, it is believed that polynucleotides and polypeptides corresponding to this gene shares structural features to type Ib membrane proteins.

**[0519]** This gene is expressed primarily in neutrophils, activated T-cells, tonsils, and fetal heart.

**[0520]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune system disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cardiovascular, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0521]** The tissue distribution neutrophils and T-cells indicates that polynucleotides and polypeptides corresponding to this gene would be useful for diagnosis and treatment of immune related disorders including, infection, inflammation, allergy, tissue/organ transplantation, immunodeficiency, etc. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. Involvement in the regulation of cytokine production, antigen presentation, or other processes indicates a usefulness for treatment of cancer (e.g., by boosting immune responses). Polynucleotides and polypeptides corresponding to this gene may have clinical relevance in the treatment of impaired immunity, in the correction of autoimmunity, in immune modulation, in the treatment of allergy, and in the regulation of inflammation. It may also play a role in influencing differentiation of specific hematopoietic lineages, and may even affect the hematopoietic stem cell. Furthermore, the protein may also be used to determine biological activity, raise

antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement.

Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0522]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:82 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1626 of SEQ ID NO:82, b is an integer of 15 to 1640, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:82, and where b is greater than or equal to a + 14.

#### **[0523] FEATURES OF PROTEIN ENCODED BY GENE NO: 73**

**[0524]** This gene is expressed primarily in hemangiopericytoma, placental tissue, and breast and endometrial tumor tissues, and, to a lesser extent, in various other normal and transformed cell types.

**[0525]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, defects and tumors of female reproductive organs. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the reproductive system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a

disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0526]** The tissue distribution in endometrial tumor tissue and placental tissue indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the study, detection and/or treatment of reproductive system disorders and neoplasias, as well as cancers of other tissues where expression of this gene has been observed. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0527]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:83 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 511 of SEQ ID NO:83, b is an integer of 15 to 525, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:83, and where b is greater than or equal to a + 14.

**[0528] FEATURES OF PROTEIN ENCODED BY GENE NO: 74**

**[0529]** In an alternative reading frame, this gene shares homology with a DNA mismatch repair proteins, including PMS 4, and PMS1 (See Accession No. R95251, gnl|PID|d1008095 and pir|JC2399|JC2399).

**[0530]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group: QKRACFPFAFCRDCQFXEXSPAMLPVQPAXL (SEQ ID NO: 402); VSAHGIWLFRS (SEQ ID NO: 403); and/or

KHAAPPASLSLSLLLHHGQKRACFPFAFCRDCQFXEXSPAMLVPQPAXL (SEQ ID NO: 404). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

This gene is expressed primarily in hematopoietic cells and tissues, such as monocytes, primary dendritic cells, and thymus; and, to a lesser extent, in brain

[0531] Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, hematopoietic diseases and/or disorders; immune dysfunction; susceptibility to infection; impaired immune surveillance; neurological disorders, and cancers which may result from increased genetic instability. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, CNS, and solid tissues, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hematopoietic, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

[0532] The tissue distribution primarily in hematopoietic cells and tissues and the homology to DNA mismatch repair proteins indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis and/or treatment of a variety of disorders, especially cancer. Representative uses are described in the “Immune Activity” and “Infectious Disease” sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the

expression of this gene product in a number of hematopoietic cells and tissues indicates that polynucleotides and polypeptides of the invention may play a role in the proliferation; differentiation; survival; and/or activation of a variety of hematopoietic lineages, particularly the monocyte/macrophage pathway. Expression of this gene product in a variety of brain tissues also indicates that polynucleotides and polypeptides of the invention may play a role in normal neuronal function or in establishment of neural connectivity. Therefore, polynucleotides and polypeptides of the invention may be useful in the treatment of neurological disorders, such as Alzheimer's or Parkinson's. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0533]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:84 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 823 of SEQ ID NO:84, b is an integer of 15 to 837, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:84, and where b is greater than or equal to a + 14.

**[0534] FEATURES OF PROTEIN ENCODED BY GENE NO: 75**

**[0535]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

MCDNLIMLRTL MRYIVFLSLQCLWGQGTHSSCYPPSPLRLPLFFFLDIKLGISN  
WPVVMQSCFALYLAGLICLTRSHEAIGRSSLSPPSSAPKVVARGVPS (SEQ ID

NO: 405). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention..

**[0536]** This gene is expressed primarily in T-cell lymphoma, endometrial tumors, and infant brain cells.

**[0537]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, T-cell lymphoma, endometrial tumor, and neurodegenerative or developmental diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune, central nervous system, and reproductive systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, immune, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one or both of the immunogenic epitopes shown in SEQ ID NO: 192 as residues: Glu-28 to Tyr-33, Gly-50 to Tyr-57. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0538]** The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for detecting, diagnosing, preventing and/or treating T-cell lymphoma, endometrial tumors, neurodegenerative or

developmental disorders. The tissue distribution in infant brain cells indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection/treatment of neurodegenerative disease states and behavioural disorders. Representative uses are described in the “Regeneration” and “Hyperproliferative Disorders” sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer’s Disease, Parkinson’s Disease, Huntington’s Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, polynucleotides and polypeptides of the invention may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0539]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:85 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1560 of SEQ ID NO:85, b is an integer of 15 to 1574, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:85, and where b is greater than or equal to a + 14.

#### **[0540] FEATURES OF PROTEIN ENCODED BY GENE NO: 76**



**[0541]** A translated product of this gene shares some homology with *C. elegans* UNC-53 protein variant 7A and 8A which would be useful to promote neuronal regeneration, revascularisation or wound healing (see, e.g., GenSeq Accession W20057 and W20056; all references available through these accessions are hereby incorporated herein by reference).

**[0542]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group: MLVLMTLFLLLYRYVYGFVCVYVHIYAHYTHTHIYNQLSIAYSSLIYILY SNFSNTPTKSFSPPYQYYNVDPDNNITNPALTPTDFFENKQLLHAISFLYSPGTGFL QPPAHPVQLRTSTTLYGNHRGQTGCSQLD (SEQ ID NO:406), and SNTPTKSFSPPYQYYNVDPDNNITNPALTPTDFFENKQLLHAISFLYSPGTGFLQPP AHPVQLRTSTTL (SEQ ID NO: 407). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0543]** This gene is expressed primarily in cancer cells, particular from hepatocellular carcinoma.

**[0544]** Homology to proteins that promote wound healing and revascularization indicate that polynucleotides and polypeptides corresponding to this gene would be useful in the detection, treatment, and/or prevention of a variety of vascular disorders and conditions, which include, but are not limited to microvascular disease, vascular leak syndrome, aneurysm, stroke, embolism, thrombosis, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Moreover, homology to proteins involved in neuronal regeneration indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly,

the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, polynucleotides and polypeptides corresponding to this gene are involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, central and peripheral nervous system tissues, wounded and healing tissues, cardiovascular system tissues, ocular tissues (particularly retina), hepatocellular carcinoma and other similar cancer, particularly of the liver. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the hepatic system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., hepatic, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0545]** The tissue distribution in tissues of cancerous origins, such as hepatocellular carcinoma tissue, indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis and/or treatment of a variety of cancers, most notably cancers of the liver, such as hepatocellular carcinoma. Expression of this

gene product in a variety of cancers indicates that polynucleotides and polypeptides corresponding to this gene may be a player in the progression of these diseases, and may be a beneficial target for inhibitors as therapeutics. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0546]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:86 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1614 of SEQ ID NO:86, b is an integer of 15 to 1628, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:86, and where b is greater than or equal to a + 14.

**[0547] FEATURES OF PROTEIN ENCODED BY GENE NO: 77**

**[0548]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group:

MEMNYCGSRVLY (SEQ ID NO: 408) and/or

MEMNYCGSRVLYMSLILLGSPILWSYTSATQAAALVTSHVWKPSLEAHQIN  
ISPEPSIHYDRWHTQSNCSLINSIQ (SEQ ID NO:409). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0549]** This gene is expressed primarily in T-cell lymphoma, and, to a lesser extent, in hepatocellular tumor tissue.

**[0550]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, T-cell lymphoma, hepatocellular tumors, and cancers. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and hepatic systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hepatic, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of the immunogenic epitopes shown in SEQ ID NO: 194 as residues: Pro-46 to Asn-58. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0551]** The tissue distribution in T-cell lymphoma and hepatocellular tumor tissue indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, diagnosis, prevention and/or treatment of T-cell lymphomas and hepatocellular tumors, as well as cancers of other tissues where expression of this gene has been observed. Representative uses are described in the “Immune Activity” and “Infectious Disease” sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0552]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are

related to SEQ ID NO:87 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1781 of SEQ ID NO:87, b is an integer of 15 to 1795, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:87, and where b is greater than or equal to a + 14.

**[0553] FEATURES OF PROTEIN ENCODED BY GENE NO: 78**

**[0554]** This gene is expressed primarily in brain tissue, and, to a lesser extent, in ntera2 cell lines, melanocytes, normal colon, and T-helper cells.

**[0555]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurodegenerative diseases and/or conditions. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, immune, hematopoietic, gastrointestinal, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of the immunogenic epitopes shown in SEQ ID NO: 195 as residues: Met-1 to Trp-6. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

[0556] The tissue distribution in brain tissue indicates that polynucleotides and polypeptides corresponding to this gene would be useful for detecting and/or treating neurodegenerative diseases of the central nervous system. Representative uses are described in the “Regeneration” and “Hyperproliferative Disorders” sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, diagnosis, prevention, and/or treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer’s Disease, Parkinson’s Disease, Huntington’s Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[0557] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:88 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1850 of SEQ ID NO:88, b is an integer of 15 to 1864, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:88, and where b is greater than or equal to a + 14.

**[0558] FEATURES OF PROTEIN ENCODED BY GENE NO: 79**

**[0559]** The gene encoding the disclosed cDNA is thought to reside on chromosome 1. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 1.

**[0560]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group: IPEEASCFPSAV (SEQ ID NO: 410), EILFGKLKSKAALCTQG (SEQ ID NO: 411), HADRYTCCRCLSPFSLAGL (SEQ ID NO: 412), LSDPLLLPDCSFSFN (SEQ ID NO: 413), KAVAYANVSCRRFKHKTTKLGPIQW (SEQ ID NO: 414), PSSQSPEPPQPLSLFVTRLPNLYDFP (SEQ ID NO: 415), and/or SRQIICTNLCKCTPICFLF (SEQ ID NO: 416). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0561]** Translated products of this gene share some homology with a Factor VIIa protein (see, e.g., GenSeq Accession No. R13788; all references available through this accession are hereby incorporated herein by reference). In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group: KGSLPWRLLLPLNGP (SEQ ID NO: 417) and LCRLVFESSAGHVSVCCHSF (SEQ ID NO: 418). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0562]** This gene is expressed primarily in breast tissue, fetal liver and adult hepatoma tissues, and, to a lesser extent, in merkel cells and osteoblasts.

**[0563]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, circulatory disorders (particularly coagulatory disorders), cancers of the liver or breast. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the circulatory system or glandular systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., breast, liver, cancerous and wounded tissues) or bodily fluids (e.g., lymph, breast milk, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of the immunogenic epitopes shown in SEQ ID NO: 196 as residues: Asn-25 to Gln-50. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0564]** The tissue distribution in breast and hepatoma tissues indicates that polynucleotides and polypeptides corresponding to this gene would be useful for diagnosing and/or treating tumors of the breast or liver. Furthermore, the expression in the breast tissue may indicate its uses in breast neoplasia and breast cancers, such as fibroadenoma, papillary carcinoma, ductal carcinoma, Paget's disease, medullary carcinoma, mucinous carcinoma, tubular carcinoma, secretory carcinoma and apocrine carcinoma, as well as juvenile hypertrophy and gynecomastia, mastitis and abscess, duct ectasia, fat necrosis and fibrocystic diseases. Alternatively, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection and treatment of liver disorders and cancers (e.g., hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). Protein, as well



as, antibodies directed against the protein may show utility as a tumor marker and immunotherapy targets for the above listed tumors and tissues.

**[0565]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:89 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1969 of SEQ ID NO:89, b is an integer of 15 to 1983, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:89, and where b is greater than or equal to a + 14.

**[0566] FEATURES OF PROTEIN ENCODED BY GENE NO: 80**

**[0567]** This gene is expressed primarily in thymus and brain tissues.

**[0568]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders of the immune system and diseases of the brain, including various types of mood disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system and central nervous system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, neural, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0569]** The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of a variety of immune system disorders. Representative uses are described in the “Immune Activity” and “Infectious Disease” sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product in thymus indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. Polynucleotides and polypeptides corresponding to this gene may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore polynucleotides and polypeptides of the invention may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, polynucleotides and polypeptides of the invention may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Alternatively, the tissue distribution in brain tissue indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, diagnosis, prevention and/or treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer’s Disease, Parkinson’s Disease, Huntington’s Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate

ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0570]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:90 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1943 of SEQ ID NO:90, b is an integer of 15 to 1957, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:90, and where b is greater than or equal to a + 14.

**[0571] FEATURES OF PROTEIN ENCODED BY GENE NO: 81**

**[0572]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group:

MLLPVNTLLYI (SEQ ID NO: 419), LLTPLCFFYGTSRP (SEQ ID NO: 420),  
PYLELVT (SEQ ID NO: 421), LLKKKKQSVGFSV (SEQ ID NO: 422), CILEAGR  
(SEQ ID NO: 423), MGFSAPTPGPL (SEQ ID NO: 424), FDLRRLILSIV (SEQ ID  
NO: 425), AFCPHVTPCKYAVIHTV (SEQ ID NO: 426), NTPLLFLWDLQ (SEQ  
ID NO: 427), ATIFRTSYLIKKEKTV (SEQ ID NO: 428),  
WLLSLHLGGREVRAGAP (SEQ ID NO: 429), QTLQEGSLHSI (SEQ ID NO:  
430), and/or

MGFSAPTPGPLFDLRRLILSIVAFCPHVTPCKYAVIHTVNTPLLFLWDLQATIF  
RTSYLIKKEKTVCWLLSLHLGGREVRAGAPQTLQEGSLHSI (SEQ ID NO:  
431). Moreover, fragments and variants of these polypeptides (such as, for example,  
fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%,  
97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by

a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0573]** This gene is expressed primarily in brain and breast tissues, and, to a lesser extent, in several other cell and tissue types including colon and liver tissues.

**[0574]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, breast and brain cancers, mood disorders, dementia, and Alzheimer's disease. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous and lactations systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, breast milk, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of the immunogenic epitopes shown in SEQ ID NO: 198 as residues: Gly-21 to Tyr-27. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0575]** The expression in breast tissue indicates that polynucleotides and/or polypeptides of the invention would be useful for diagnosis, treatment and/or prevention of breast neoplasia and breast cancers, such as fibroadenoma, papillary carcinoma, ductal carcinoma, Paget's disease, medullary carcinoma, mucinous carcinoma, tubular carcinoma, secretory carcinoma and apocrine carcinoma, as well as juvenile hypertrophy and gynecomastia, mastitis and abscess, duct ectasia, fat necrosis and fibrocystic diseases. Representative uses are described in the

“Regeneration” and “Hyperproliferative Disorders” sections below, in Example 11, 15, and 18, and elsewhere herein. Alternatively, the tissue distribution of this gene in brain tissue indicates that polynucleotides and polypeptides of the invention would be useful for the detection and/or treatment of brain cancers and neural disorders, such as Alzheimer’s Disease, Parkinson’s Disease, Huntington’s Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, the gene or gene product may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[0576] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:91 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 559 of SEQ ID NO:91, b is an integer of 15 to 573, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:91, and where b is greater than or equal to a + 14.

#### **[0577] FEATURES OF PROTEIN ENCODED BY GENE NO: 82**

[0578] The gene encoding the disclosed cDNA is believed to reside on chromosome 1. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 1.

**[0579]** This gene is expressed primarily in liver and, to a lesser extent, in other tissues.

**[0580]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, liver/hepatocyte disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the liver, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., liver, cancerous and wounded tissues) or bodily fluids (e.g., lymph, bile, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0581]** The tissue distribution in liver indicates that polynucleotides and polypeptides corresponding to this gene would be useful for detection, treatment, and/or prevention of liver (hepatocyte) disorders and cancers (e.g., hepatoblastoma, jaundice, hepatitis, liver metabolic diseases and conditions that are attributable to the differentiation of hepatocyte progenitor cells). Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0582]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:92 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention

are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1198 of SEQ ID NO:92, b is an integer of 15 to 1212, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:92, and where b is greater than or equal to a + 14.

**[0583] FEATURES OF PROTEIN ENCODED BY GENE NO: 83**

**[0584]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

YWVSISQRSVCQQARTSIFFKDGLSREKYSNNG (SEQ ID NO: 432). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0585]** This gene is expressed primarily in T cells.

**[0586]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune disorders, including AIDS and various other diseases in which the immune system is suppressed. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene

expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0587]** The tissue distribution in T cells indicates that the polypeptides or polynucleotides would be useful for treatment, prophylaxis, and diagnosis of immune and autoimmune diseases, such as lupus, transplant rejection, allergic reactions, arthritis, asthma, immunodeficiency diseases, leukemia, and AIDS. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. Involvement in the regulation of cytokine production, antigen presentation, or other processes indicates a usefulness for treatment of cancer (e.g., by boosting immune responses). Expression in cells of lymphoid origin, indicates the natural gene product would be involved in immune functions. Therefore polynucleotides and polypeptides of the invention would also be useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, polynucleotides and polypeptides of the invention are thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. The polypeptides or polynucleotides of the present invention would also be useful in the treatment, prophylaxis, and detection of thymus disorders, such as Grave's Disease, lymphocytic thyroiditis, hyperthyroidism, and hypothyroidism. Similarly, elevated levels of expression of this gene product in T cell lineages



indicates that it may play an active role in normal T cell function and in the regulation of the immune response. For example, this gene product may be involved in T cell activation, in the activation or control of differentiation of other hematopoietic cell lineages, in antigen recognition, or in T cell proliferation. Furthermore, the protein may also be used to determine biological activity, raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0588]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:93 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1130 of SEQ ID NO:93, b is an integer of 15 to 1144, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:93, and where b is greater than or equal to a + 14.

**[0589] FEATURES OF PROTEIN ENCODED BY GENE NO: 84**

**[0590]** The translation product of this gene shares sequence homology with a protein which was found to accumulate during growth-factor-induced proliferation and transformation of normal rat fibroblasts (see, e.g., Glaichenhaus, N., and Cuzin, F., Cell 50:1081 (1987); and Genbank Acc. No. gi|207250; all references available through this accession and reference are hereby incorporated by reference herein.)

**[0591]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group:

LSVRAPGVPAARPLSSARQAGAGRGELRGQRLWLGPECGCGAGQAGSMLR  
AVGSLRLRGLTVRCGPGAPLEATRRPAPALPPRGLPCYSSGGAPSNSGPQG

HGEIHRVPTQRRPSQFDKKILLWTGRFKSMEEIPPRIPPEMIDTARNKARVKAC  
 YI (SEQ ID NO:433), LSVRAPGVPAARPRLLSSARQAGAGRGELRGQRLWL  
 G (SEQ ID NO:434), PECGCGAGQAGSMLRAVGSLRLGRGLTVRCGPG (SEQ ID  
 NO:435), APLEATRRPAPALPPRGLPCYSSGGAPSNSGPQG (SEQ ID NO:436),  
 HGEIHRVPTQRRPSQFDKKILLWTGRF (SEQ ID NO:437), and/or  
 KSMEEIPPRIPPEMIDTARNKARVKACYI (SEQ ID NO:438). Moreover,  
 fragments and variants of these polypeptides (such as, for example, fragments as  
 described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%,  
 or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide  
 which hybridizes, under stringent conditions, to the polynucleotide encoding these  
 polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of  
 the invention and polynucleotides encoding these polypeptides are also encompassed  
 by the invention.

**[0592]** The polypeptide of this gene has been determined to have a transmembrane  
 domain at about amino acid position 4 to about 20 of the amino acid sequence  
 referenced in Table 1 for this gene. Moreover, a cytoplasmic tail encompassing amino  
 acids 1 to 3 of this protein has also been determined. Based upon these characteristics,  
 it is believed that polynucleotides and polypeptides corresponding to this gene shares  
 structural features to type II membrane proteins.

**[0593]** This gene is expressed primarily in placenta.

**[0594]** Polynucleotides and polypeptides of the invention would be useful as reagents  
 for differential identification of the tissue(s) or cell type(s) present in a biological  
 sample and for diagnosis of diseases and conditions which include, but are not limited  
 to, developmental anomalies or fetal deficiencies, cancers or neoplastic conditions.  
 Similarly, polypeptides and antibodies directed to these polypeptides would be useful  
 in providing immunological probes for differential identification of the tissue(s) or  
 cell type(s). For a number of disorders of the above tissues or cells, particularly of the  
 developing embryo, expression of this gene at significantly higher or lower levels  
 may be routinely detected in certain tissues or cell types (e.g., embryonic, placental,  
 cancerous and wounded tissues) or bodily fluids (e.g., lymph, amniotic fluid, serum,  
 plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken

from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0595]** The tissue distribution and homology to a protein which was found to accumulate during proliferation and transformation of normal fibroblasts indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the treatment and diagnosis of developmental anomalies or fetal deficiencies, neoplasms and cancers. Additionally, the tissue distribution in placenta indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis and/or treatment of disorders of the placenta. Specific expression within the placenta indicates that polynucleotides and polypeptides of the invention may play a role in the proper establishment and maintenance of placental function. Alternately, polynucleotides and polypeptides of the invention may be produced by the placenta and then transported to the embryo, where it may play a crucial role in the development and/or survival of the developing embryo or fetus. Expression of this gene product in a vascular-rich tissue such as the placenta also indicates that polynucleotides and polypeptides of the invention may be produced more generally in endothelial cells or within the circulation. In such instances, it may play more generalized roles in vascular function, such as in angiogenesis. Polynucleotides and polypeptides of the invention may also be produced in the vasculature and have effects on other cells within the circulation, such as hematopoietic cells. It may serve to promote the proliferation, survival, activation, and/or differentiation of hematopoietic cells, as well as other cells throughout the body. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0596]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:94 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1260 of SEQ ID NO:94, b is an integer of 15 to 1274, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:94, and where b is greater than or equal to a + 14.

**[0597] FEATURES OF PROTEIN ENCODED BY GENE NO: 85**

**[0598]** The translated product of this gene shares some homology with a novel alpha-neurotoxin from the king cobra (*Ophiophagus hannah*) venom (see, e.g., Genbank Accession No. JC1474 and P80965; all references available through these accessions are hereby incorporated herein by reference). Based on the sequence similarity, the translation product of this clone is expected to share at least some biological activities with neurotransmitter proteins.

**[0599]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group:

CSPGQDEMQDETWC SGQSETVNEAKQLRTTHSRVPNQVCVCGWLPVNISP  
HSPLKK (SEQ ID NO: 439) and/or

MSGDVCVFGY AHLHSQTKHSGSQGWVLIYLFAMQKISCTKLPLLRNLKLN  
VWLSQGWVFFKGLWGEMLTGSHPQTHTCWLGTRLWVVLSC LASLTVSDCP  
EHQVSSCISSWPGEHSVSFQFPFPHSLGGTEVGVEESQMAGVGI (SEQ ID

NO: 440). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention.

Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0600]** The gene encoding the disclosed cDNA is thought to reside on chromosome 3. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 3.

**[0601]** This gene is expressed primarily in T-cell lymphoma and synovial sarcoma tissues, and, to a lesser extent, in fetal liver/spleen tissue and synovial fibroblasts.

**[0602]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, T-Cell lymphoma and synovial sarcoma. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one or both of the immunogenic epitopes shown in SEQ ID NO: 202 as residues: Gly-4 to His-10, Asp-32 to Val-38. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0603]** The tissue distribution in T-cell lymphoma and synovial sarcoma tissues indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, diagnosis, prevention and/or treatment of T-cell lymphomas and synovial sarcomas, as well as cancers of other tissues where expression of this gene has been observed. Representative uses are described in the “Immune Activity” and “Infectious Disease” sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Furthermore, the protein may also be used to determine

biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0604]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:95 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1766 of SEQ ID NO:95, b is an integer of 15 to 1780, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:95, and where b is greater than or equal to a + 14.

**[0605] FEATURES OF PROTEIN ENCODED BY GENE NO: 86**

**[0606]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group: LNILISLTVSSHCKL (SEQ ID NO: 441), INYHSGFIHQFLA (SEQ ID NO: 442), and/or MANNSLSSQFI (SEQ ID NO: 443). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0607]** The translated product of this gene shares some homology with Integrin Beta 5 subunit protein (see, e.g., GenBank Accession No. Q64657; all references available through this accession are hereby incorporated herein by reference).

**[0608]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:  
ISGVLIFNLIASSWVLCFPLCDLSCQKTLRIFFASFFHAVCVHVSCTSWQPLVLF  
IKWWVVGCS (SEQ ID NO: 444). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0609]** The translated product of this gene also contains a Zinc finger (C2H2 type) domain consistent with the consensus pattern:

C.{2,4}C.{3}[LIVMFYWC].{8}H.{3,5}H (identified using the ProSite analysis tool (Swiss Institute of Bioinformatics)). Accordingly, in specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence: CDLSCQKTLRIFFASFFHAVCVH (SEQ ID NO: 445). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0610]** This gene is expressed primarily in thymus tissue.

**[0611]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases and/or disorders of the immune system. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression

of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0612]** The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of a variety of immune system disorders. Representative uses are described in the “Immune Activity” and “Infectious Disease” sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product in thymus indicates a role in the regulation of the proliferation; survival; differentiation; and/or activation of potentially all hematopoietic cell lineages, including blood stem cells. Polynucleotides and polypeptides corresponding to this gene may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore polynucleotides and polypeptides of the invention may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, polynucleotides and polypeptides of the invention may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.



**[0613]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:96 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1780 of SEQ ID NO:96, b is an integer of 15 to 1794, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:96, and where b is greater than or equal to a + 14.

**[0614] FEATURES OF PROTEIN ENCODED BY GENE NO: 87**

**[0615]** The gene encoding the disclosed cDNA is believed to reside on chromosome 10. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 10.

**[0616]** This gene is expressed primarily in brain, kidney, testes, colon cancer, parathyroid tumor, immune cells (e.g., T-cells) and to a lesser extent, in many other tissues.

**[0617]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, kidney diseases and various diseases of the brain including mood disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain and renal systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., kidney, CNS, immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or cerebrospinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e.,

the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of the immunogenic epitopes shown in SEQ ID NO: 204 as residues: Arg-68 to Lys-78. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0618]** The tissue distribution in kidney indicates that polynucleotides and polypeptides corresponding to this gene would be useful in the treatment, prevention, diagnosis and/or detection of kidney diseases including renal failure, nephritis, renal tubular acidosis, proteinuria, pyuria, edema, pyelonephritis, hydronephritis, nephrotic syndrome, crush syndrome, glomerulonephritis, hematuria, renal colic and kidney stones, in addition to Wilm's Tumor Disease, and congenital kidney abnormalities such as horseshoe kidney, polycystic kidney, and Falconi's syndrome. The tissue distribution in brain indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, this gene product is involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. The tissue distribution in testes, kidney, and other tissues associates with the endocrine system indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of various endocrine disorders

and cancers. Representative uses are described in the "Biological Activity", "Hyperproliferative Disorders", and "Binding Activity" sections below, in Example 11, 17, 18, 19, 20 and 27, and elsewhere herein. Briefly, the protein can be used for the detection, treatment, and/or prevention of Addison's disease, Cushing's Syndrome, and disorders and/or cancers of the pancreas (e.g., diabetes mellitus), adrenal cortex, ovaries, pituitary (e.g., hyper-, hypopituitarism), thyroid (e.g., hyper-, hypothyroidism), parathyroid (e.g., hyper-, hypoparathyroidism), hypothalamus, and testes. The tissue distribution in immune cells (e.g., T-cells) indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. Involvement in the regulation of cytokine production, antigen presentation, or other processes indicates a usefulness for treatment of cancer (e.g. by boosting immune responses). Expression in cells of lymphoid origin, indicates the natural gene product would be involved in immune functions. Therefore it would also be useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue

markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0619]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:97 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 2051 of SEQ ID NO:97, b is an integer of 15 to 2065, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:97, and where b is greater than or equal to a + 14.

#### **[0620] FEATURES OF PROTEIN ENCODED BY GENE NO: 88**

**[0621]** It has been discovered that this gene is expressed primarily in neutrophils.

**[0622]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, immune and inflammatory disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune and inflammatory systems, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the

present invention comprise, or alternatively consist of the immunogenic epitopes shown in SEQ ID NO: 205 as residues: Pro-41 to Gln-48. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0623]** The tissue distribution in neutrophils indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the study, diagnosis, detection prevention and/or treatment of immune and inflammatory diseases. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. Furthermore, polynucleotides and polypeptides of the invention may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore polynucleotides and polypeptides of the invention may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0624]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:98 and may have been publicly available prior to conception of

the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1140 of SEQ ID NO:98, b is an integer of 15 to 1154, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:98, and where b is greater than or equal to a + 14.

**[0625] FEATURES OF PROTEIN ENCODED BY GENE NO: 89**

**[0626]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence: ELAIGESCS (SEQ ID NO: 446). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0627]** The translation product of this gene shares sequence homology with NY-REN-8 antigen (see, e.g., Genbank accession number AF155098 (AD42864); all references available through this accession are hereby incorporated by reference herein) which is an antigen recognized by autologous antibody in patients with renal-cell carcinoma and may be important in cancer diagnosis, therapy, and/or prevention. Based on the sequence similarity, the translation product of this clone is expected to share at least some biological activities with NY-REN-8 antigen and other related antigens.

**[0628]** This gene is expressed primarily in brain, testes, and fetal tissue.

**[0629]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited

to, developmental, degenerative and behavioral diseases of the brain such as schizophrenia, Alzheimer's disease, Parkinson's disease, Huntington's disease, transmissible spongiform encephalopathies (TSE), Creutzfeldt-Jakob disease (CJD), specific brain tumors, aphasia, mania, depression, dementia, paranoia, addictive behavior and sleep disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the brain, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., CNS, endocrine, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or cerebrospinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of the immunogenic epitopes shown in SEQ ID NO: 206 as residues: Gly-45 to Thr-50. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0630]** The tissue distribution in brain indicates polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated

expression of this gene product in regions of the brain indicates that polynucleotides and polypeptides of the invention may play a role in normal neural function. Potentially, polynucleotides and polypeptides of the invention are involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. Moreover, the expression within fetal tissue and other cellular sources marked by proliferating cells indicates that polynucleotides and polypeptides of the invention may play a role in the regulation of cellular division, and may show utility in the diagnosis, treatment, and/or prevention of developmental diseases and disorders, including cancer, and other proliferative conditions. Representative uses are described in the "Hyperproliferative Disorders" and "Regeneration" sections below and elsewhere herein. Briefly, developmental tissues rely on decisions involving cell differentiation and/or apoptosis in pattern formation. Dysregulation of apoptosis can result in inappropriate suppression of cell death, as occurs in the development of some cancers, or in failure to control the extent of cell death, as is believed to occur in acquired immunodeficiency and certain degenerative disorders, such as spinal muscular atrophy (SMA). Alternatively, polynucleotides and polypeptides of the invention may be involved in the pattern of cellular proliferation that accompanies early embryogenesis. Thus, aberrant expression of this gene product in tissues - particularly adult tissues - may correlate with patterns of abnormal cellular proliferation, such as found in various cancers. Because of potential roles in proliferation and differentiation, polynucleotides and polypeptides of the invention may have applications in the adult for tissue regeneration and the treatment of cancers. It may also act as a morphogen to control cell and tissue type specification. Therefore, the polynucleotides and polypeptides of the present invention would be useful in treating, detecting, and/or preventing said disorders and conditions, in addition to other types of degenerative conditions. Thus polynucleotides and polypeptides of the invention may modulate apoptosis or tissue differentiation and would be useful in the detection, treatment, and/or prevention of degenerative or proliferative conditions and diseases. Polynucleotides and polypeptides of the invention would be useful in modulating the immune response to aberrant polypeptides, as may exist in proliferating and cancerous cells and tissues. The



protein can also be used to gain new insight into the regulation of cellular growth and proliferation. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[0631] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:99 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 601 of SEQ ID NO:99, b is an integer of 15 to 615, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:99, and where b is greater than or equal to a + 14.

#### **[0632] FEATURES OF PROTEIN ENCODED BY GENE NO: 90**

[0633] The gene encoding the disclosed cDNA is believed to reside on chromosome 3. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 3.

[0634] This gene is expressed primarily in brain tissue, kidney, tonsils, bone marrow, colon, testes, ovary tumor, and to a lesser extent many other tissues.

[0635] Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, neurological and behavioural disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the central nervous system, expression of

this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., CNS, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or cerebrospinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

[0636] The tissue distribution in brain indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, treatment, and/or prevention of neurodegenerative disease states, behavioral disorders, or inflammatory conditions. Representative uses are described in the "Regeneration" and "Hyperproliferative Disorders" sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the uses include, but are not limited to the detection, treatment, and/or prevention of Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, meningitis, encephalitis, demyelinating diseases, peripheral neuropathies, neoplasia, trauma, congenital malformations, spinal cord injuries, ischemia and infarction, aneurysms, hemorrhages, schizophrenia, mania, dementia, paranoia, obsessive compulsive disorder, depression, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, elevated expression of this gene product in regions of the brain indicates it plays a role in normal neural function. Potentially, polynucleotides and polypeptides of the invention are involved in synapse formation, neurotransmission, learning, cognition, homeostasis, or neuronal differentiation or survival. The tissue distribution in bone marrow and other immune tissues indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis and treatment of a variety of immune system disorders. Representative uses are described in the "Immune Activity" and "Infectious Disease" sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression indicates a role in regulating the proliferation; survival; differentiation; and/or activation of hematopoietic cell lineages, including blood stem cells. Involvement in the regulation of cytokine production, antigen presentation, or other processes indicates a usefulness

for treatment of cancer (e.g., by boosting immune responses). Expression in cells of lymphoid origin, indicates the natural gene product would be involved in immune functions. Therefore polynucleotides and polypeptides of the invention would also be useful as an agent for immunological disorders including arthritis, asthma, immunodeficiency diseases such as AIDS, leukemia, rheumatoid arthritis, granulomatous disease, inflammatory bowel disease, sepsis, acne, neutropenia, neutrophilia, psoriasis, hypersensitivities, such as T-cell mediated cytotoxicity; immune reactions to transplanted organs and tissues, such as host-versus-graft and graft-versus-host diseases, or autoimmunity disorders, such as autoimmune infertility, lense tissue injury, demyelination, systemic lupus erythematosus, drug induced hemolytic anemia, rheumatoid arthritis, Sjogren's disease, and scleroderma. Moreover, the protein may represent a secreted factor that influences the differentiation or behavior of other blood cells, or that recruits hematopoietic cells to sites of injury. Thus, this gene product is thought to be useful in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[0637] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:100 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1610 of SEQ ID NO:100, b is an integer of 15 to 1624, where both a and b correspond to the positions of

nucleotide residues shown in SEQ ID NO:100, and where b is greater than or equal to a + 14.

**[0638] FEATURES OF PROTEIN ENCODED BY GENE NO: 91**

**[0639]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

PVIWPDGKRIVLLAEVS (SEQ ID NO: 447). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0640]** This gene is expressed primarily in adrenal gland tumor.

**[0641]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, adrenal gland cancer. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the adrenal system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., adrenal gland, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of the immunogenic epitopes shown in SEQ ID NO: 208 as residues: Arg-49 to Gln-56. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0642]** The tissue distribution in adrenal gland indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis, detection, prevention and/or treatment of disorders involving the adrenal gland. Expression of this gene product in adrenal gland tumor indicates that polynucleotides and polypeptides of the invention may play a role in the proliferation of cells of the adrenal gland, or potentially in the proliferation of cells in general. In such an event, it may play a role in determining the course and severity of cancer. Alternatively, polynucleotides and polypeptides of the invention may play a role in the normal function of adrenal glands, such as in the production of corticosteroids, androgens, or epinephrines. Thus polynucleotides and polypeptides of the invention may play a role in general homeostasis, as well as in disorders involving the androgen hormones. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0643]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:101 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1742 of SEQ ID NO:101, b is an integer of 15 to 1756, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:101, and where b is greater than or equal to a + 14.

**[0644] FEATURES OF PROTEIN ENCODED BY GENE NO: 92**

**[0645]** The gene encoding the disclosed cDNA is thought to reside on chromosome 2. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 2.

**[0646]** This gene is expressed in multiple tissues, including the thymus, and cell types, including B cells and monocytes.

**[0647]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, disorders and/or disorders afflicting the immune system, such as AIDS and autoimmune diseases. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0648]** The tissue distribution in immune system tissues and cells indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis, detection, prevention and/or treatment of disorders affecting the immune system, especially autoimmune diseases and AIDS. Representative uses are described in the “Immune Activity” and “Infectious Disease” sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, polynucleotides and polypeptides of the invention may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore polynucleotides and polypeptides of the invention may be also used as an agent for immunological

disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis, inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, this gene product may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0649]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:102 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1402 of SEQ ID NO:102, b is an integer of 15 to 1416, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:102, and where b is greater than or equal to a + 14.

**[0650] FEATURES OF PROTEIN ENCODED BY GENE NO: 93**

**[0651]** The translated product of this gene shares some homology with an X-linked retinopathy protein (see, e.g., Genbank Accession No. AAB26149.1 and Wong, P., et al., Genomics 15(3):467-71 (1993); all references available through this accession and citation are hereby incorporated herein by reference).

**[0652]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group: FYYFWRQGGSCFVQTGVQWCDHGSLQL (SEQ ID NO: 448) and TPGRQSKTPS (SEQ ID NO: 449). Moreover, fragments and variants of these

polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention. [0653] The translated product of this gene also shares some homology with a Human histiocyte-secreted factor (HSF) protein (see, e.g., GenSeq Accession No. R96800; all references available through this accession are hereby incorporated herein by reference).

[0654] In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

YFIIFGDREGLALFRLECSGVIMAHCNFELLGDR (SEQ ID NO: 450). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

[0655] This gene is expressed primarily in fetal lung tissue.

[0656] Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to ocular, immune, and lung diseases and/or disorders. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the eye (especially retina), immune system, and lung, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., retina, blood, pulmonary, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum,



plasma, urine, sputum, pulmonary surfactant, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of the immunogenic epitopes shown in SEQ ID NO: 210 as residues: Leu-32 to His-38. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

[0657] The tissue distribution in fetal lung tissue indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, diagnosis, prevention and/or treatment of lung diseases and/or disorders. Representative uses are described elsewhere herein. Furthermore, the tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection and treatment of disorders associated with developing lungs, particularly in premature infants where the lungs are the last tissues to develop. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis and intervention of lung tumors, since the gene may be involved in the regulation of cell division, particularly since it is expressed in fetal tissue. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[0658] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:103 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 690 of SEQ ID NO:103, b

is an integer of 15 to 704, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:103, and where b is greater than or equal to a + 14.

**[0659] FEATURES OF PROTEIN ENCODED BY GENE NO: 94**

**[0660]** The translated product of this gene shares some homology with peripheral benzodiazepine receptor interacting protein (see Genbank Accession No. AAD11957.1; all references available through this accession are hereby incorporated herein by reference).

**[0661]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, an amino acid sequence selected from the group: CFLSVSFQWN (SEQ ID NO: 451), VTIAQVGIFVCFVHCCT (SEQ ID NO: 452), PGQVPSKHLGSNASVRA (SEQ ID NO: 453), DEGAKVQRRPWGSQTHSPVLFL (SEQ ID NO: 454), LTRPGLWGSLLPVQQQRG (SEQ ID NO: 455), CASLGVLNRANRSPCV (SEQ ID NO: 456), SWLEVTTLSAPGPVITTY (SEQ ID NO: 457), PGQWVREIXLVGRAVARV (SEQ ID NO: 458), LTWPPXGPMGTVWPGF (SEQ ID NO: 459), MADIPGTFLALGCHGQR (SEQ ID NO: 460), VGRGSWASGWTNQSA (SEQ ID NO: 461), PDHPLPVGLLEAWRVE (SEQ ID NO: 462) and/or WGSQTHSPVLFLLTRPGLWGSLLPVQQQRGCASLGVLNRANRSPCVSWLEVTTLSAPGPVITTYPGQWVREIXLVGRAVARVLTWPPXGPMGTVWPGFMADIPGTFLALGCHGQRVGRGSWASGWTNQ-SAFPAGPPDHPLPV (SEQ ID NO: 463). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0662]** This gene is expressed primarily neutrophils and eosinophils, and, to a lesser extent, in bone marrow and fetal liver/spleen tissue.

**[0663]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, asthma and diseases and/or disorders afflicting the immune system. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of the immunogenic epitopes shown in SEQ ID NO: 211 as residues: Ser-2 to Trp-7. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0664]** The tissue distribution in immune system cells and tissues indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis, detection, prevention and/or treatment of asthma or other disorders affecting the immune system. Representative uses are described in the “Immune Activity” and “Infectious Disease” sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, polynucleotides and polypeptides of the invention may be involved in the regulation of cytokine production, antigen presentation, or other processes that may also suggest a usefulness in the treatment of cancer (e.g., by boosting immune responses). Since the gene is expressed in cells of lymphoid origin, the gene or protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues. Therefore polynucleotides and polypeptides of the invention may be also used as an agent for immunological disorders including arthritis, asthma, immune deficiency diseases such as AIDS, leukemia, rheumatoid arthritis,

inflammatory bowel disease, sepsis, acne, and psoriasis. In addition, polynucleotides and polypeptides of the invention may have commercial utility in the expansion of stem cells and committed progenitors of various blood lineages, and in the differentiation and/or proliferation of various cell types. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[0665] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:104 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1245 of SEQ ID NO:104, b is an integer of 15 to 1259, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:104, and where b is greater than or equal to a + 14.

#### **[0666] FEATURES OF PROTEIN ENCODED BY GENE NO: 95**

[0667] This gene shares sequence homology to the rat cornichon-like protein (see, e.g., Genbank Accession No. 2317276), the murine cornichon protein (see, e.g., Genbank Accession No. gi|2460430), and the human cornichon protein (see, e.g., Genbank Accession No. gi|4063709). All references available through these accessions are hereby incorporated by reference herein. The *Drosophila* cornichon gene is thought to be involved in signaling processes necessary for both anterior-posterior and dorsal-ventral pattern formation in *Drosophila*. Thus, it is likely that this gene plays a similar role in human development.

**[0668]** The gene encoding the disclosed cDNA is thought to reside on chromosome 1. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 1.

**[0669]** This gene is expressed primarily in endometrial tumor tissue and infant brain tissue, and, to a lesser extent, in frontal cortex tissue.

**[0670]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, endometrial tumor, and neural and developmental diseases and/or disorders.

Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the neural and reproductive organs, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., neural, reproductive, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, amniotic fluid, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of the immunogenic epitopes shown in SEQ ID NO: 212 as residues: Glu-33 to Phe-38. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0671]** The tissue distribution in infant brain tissue and frontal cortex tissue, and the homology to cornichon proteins, indicates that polynucleotides and polypeptides corresponding to this gene would be useful for detecting, diagnosing, preventing and/or treating neural and developmental disorders. The tissue distribution indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection, diagnosis, prevention and/or treatment of neurodegenerative disease states and behavioural disorders such as Alzheimer's Disease, Parkinson's Disease, Huntington's Disease, Tourette Syndrome, schizophrenia, mania, dementia, paranoia,

obsessive compulsive disorder, panic disorder, learning disabilities, ALS, psychoses, autism, and altered behaviors, including disorders in feeding, sleep patterns, balance, and perception. In addition, polynucleotides and polypeptides of the invention may also play a role in the treatment and/or detection of developmental disorders associated with the developing embryo, or sexually-linked disorders. Representative uses are described in the “Regeneration” and “Hyperproliferative Disorders” sections below, in Example 11, 15, and 18, and elsewhere herein. Briefly, the elevated expression of this gene product within the frontal cortex of the brain indicates that polynucleotides and polypeptides of the invention may be involved in neuronal survival; synapse formation; conductance; neural differentiation, etc. Such involvement may impact many processes, such as learning and cognition. Alternatively, the tissue distribution in endometrial tumor tissue indicates that polynucleotides and polypeptides of the invention would be useful for the detection and/or treatment of endometrial tumors and/or reproductive disorders, as well as tumors of other tissues where expression of this gene has been observed. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[0672] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:105 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 1790 of SEQ ID NO:105, b is an integer of 15 to 1804, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:105, and where b is greater than or equal to a + 14.

**[0673] FEATURES OF PROTEIN ENCODED BY GENE NO: 96**

**[0674]** The translation product of this gene shares significant sequence homology with a protein which was recently sequenced by another group, which was named paraplegin by this group (see, e.g., Genbank Accession No. g3273089).

**[0675]** The gene encoding the disclosed cDNA is thought to reside on chromosome 16. Accordingly, polynucleotides related to this invention would be useful as a marker in linkage analysis for chromosome 16.

**[0676]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence:

LARADPPGCRRRGWRPSSAELQLRLLTPTFEGINGLLKQHLVQNPVRLWQL  
LGGTFYFNTSRLKQKNKE KDKSKGKAPEEDEXERRRRERDDQ (SEQ ID NO:  
464). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0677]** When tested against Jurkat T-cell cell lines, supernatants removed from cells containing this gene activated the GAS assay. Thus, it is likely that this gene activates T-cells, and to a lesser extent other immune cells, through the Jak-STAT signal transduction pathway. The gamma activating sequence (GAS) is a promoter element found upstream of many genes which are involved in the Jak-STAT pathway. The Jak-STAT pathway is a large, signal transduction pathway involved in the differentiation and proliferation of cells. Therefore, activation of the Jak-STAT pathway, reflected by the binding of the GAS element, can be used to indicate proteins involved in the proliferation and differentiation of cells.

**[0678]** This gene is expressed primarily in Jurkat T-cells, Macrophage, T-Cell Lymphoma, tonsils, and salivary glands.

**[0679]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, T-Cell lymphomas. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the immune system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., immune, hematopoietic, and cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid or spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder. Preferred polypeptides of the present invention comprise, or alternatively consist of one, two, three, four, five, six or all seven of the immunogenic epitopes shown in SEQ ID NO: 213 as residues: Met-1 to Leu-6, Asp-84 to Lys-89, Asp-124 to Gly-130, Ser-138 to Trp-143, His-145 to Ser-153, Thr-170 to Pro-183, Trp-191 to Pro-198. Polynucleotides encoding said polypeptides are encompassed by the invention, as are antibodies that bind one or more of these peptides.

**[0680]** The tissue distribution in immune tissues and T-cells, in conjunction with the detected GAS biological activity data, indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the detection and/or treatment of T-cell lymphomas. Representative uses are described in the “Immune Activity” and “Infectious Disease” sections below, in Example 11, 13, 14, 16, 18, 19, 20, and 27, and elsewhere herein. Briefly, the expression of this gene product in T cell lymphoma indicates that polynucleotides and polypeptides of the invention may play a role in the proliferation of the lymphoid cell lineages, and may be involved in normal antigen recognition and activation of T cells during the immune process. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as,



antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

**[0681]** Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:106 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 957 of SEQ ID NO:106, b is an integer of 15 to 971, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:106, and where b is greater than or equal to a + 14.

**[0682] FEATURES OF PROTEIN ENCODED BY GENE NO: 97**

**[0683]** In specific embodiments, polypeptides of the invention comprise, or alternatively consist of, the following amino acid sequence: FLRFWCTCHVSS (SEQ ID NO: 465). Moreover, fragments and variants of these polypeptides (such as, for example, fragments as described herein, polypeptides at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99%, or 100% identical to these polypeptides, or polypeptides encoded by a polynucleotide which hybridizes, under stringent conditions, to the polynucleotide encoding these polypeptides) are encompassed by the invention. Antibodies that bind polypeptides of the invention and polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0684]** This gene is expressed primarily in bladder, dermal endothelial cells, retina, and dendritic cells.

**[0685]** Polynucleotides and polypeptides of the invention would be useful as reagents for differential identification of the tissue(s) or cell type(s) present in a biological sample and for diagnosis of diseases and conditions which include, but are not limited to, diseases of the bladder, including bladder cancer. Similarly, polypeptides and antibodies directed to these polypeptides would be useful in providing immunological

probes for differential identification of the tissue(s) or cell type(s). For a number of disorders of the above tissues or cells, particularly of the urinary system, expression of this gene at significantly higher or lower levels may be routinely detected in certain tissues or cell types (e.g., bladder, cancerous and wounded tissues) or bodily fluids (e.g., lymph, serum, plasma, urine, synovial fluid and spinal fluid) or another tissue or cell sample taken from an individual having such a disorder, relative to the standard gene expression level, i.e., the expression level in healthy tissue or bodily fluid from an individual not having the disorder.

**[0686]** The tissue distribution in bladder indicates that the polynucleotides and polypeptides corresponding to this gene would be useful for treatment, prevention, detection and/or diagnosis of urinary tract disorders (e.g., cystitis, urinary tract calculi, incontinence) and bladder tumors or cancers. The tissue distribution in endothelial cells indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the diagnosis, detection, prevention and/or treatment of disorders involving the vasculature and/or dermal tissue. Elevated expression of this gene product by endothelial cells indicates that it may play vital roles in the regulation of endothelial cell function; secretion; proliferation; or angiogenesis. Alternately, this may represent a gene product expressed by the endothelium and transported to distant sites of action on a variety of target organs. Expression of this gene product by hematopoietic cells also indicates involvement in the proliferation; survival; activation; or differentiation of all blood cell lineages. The tissue distribution in retina indicates that polynucleotides and polypeptides corresponding to this gene would be useful for the treatment, prevention, diagnosis and/or detection of eye disorders including blindness, color blindness, impaired vision, short and long sightedness, retinitis pigmentosa, retinitis proliferans, and retinoblastoma, retinochoroiditis, retinopathy and retinoschisis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue markers, to isolate cognate ligands or receptors, to identify agents that modulate their interactions, in addition to its use as a nutritional supplement. Protein, as well as, antibodies directed against the protein may show utility as a tumor marker and/or immunotherapy targets for the above listed tissues.

[0687] Many polynucleotide sequences, such as EST sequences, are publicly available and accessible through sequence databases. Some of these sequences are related to SEQ ID NO:107 and may have been publicly available prior to conception of the present invention. Preferably, such related polynucleotides are specifically excluded from the scope of the present invention. To list every related sequence would be cumbersome. Accordingly, preferably excluded from the present invention are one or more polynucleotides comprising a nucleotide sequence described by the general formula of a-b, where a is any integer between 1 to 807 of SEQ ID NO:107, b is an integer of 15 to 821, where both a and b correspond to the positions of nucleotide residues shown in SEQ ID NO:107, and where b is greater than or equal to  $a + 1$ .

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
1	HKABZ65	209683 3/20/98	pCMVSPORT 2.0	11	1191	1	1191	69	69	118	1	17	18	243
2	HNGIC80	209683 3/20/98	Uni-ZAP XR	12	1251	1	1251	24	24	119	1	24	25	41
3	HDPUG50	209745 4/07/98	pCMVSPORT 3.0	13	1734	1	1734	22	22	120	1	34	35	526
4	HAEAB66	209745 4/07/98	pBluescript SK-	14	1540	914	1537	105	105	121	1	30	31	354
5	HHEPF59	209746 4/07/98	pCMVSPORT 3.0	15	1558	1	1558	38	38	122	1	21	22	63
6	HE9BK23	209683 3/20/98	Uni-ZAP XR	16	1636	1	1636	39	39	123	1	21	22	309
7	HCYBI36	209683 3/20/98	pBluescript SK-	17	1256	148	1256	235	235	124	1	23	24	211
8	HSSDX51	209683 3/20/98	Uni-ZAP XR	18	1143	1	1143	133	133	125	1	20	21	50
9	HSDAJ46	209746 4/07/98	Uni-ZAP XR	19	1537	92	1537	299	299	126	1	18	19	262
10	HRACG45	209745 4/07/98	pCMVSPORT 3.0	20	2672	222	2672	178	178	127	1	42	43	270
11	HAPPW30	209683 3/20/98	Uni-ZAP XR	21	1508	14	1501	54	54	128	1	22	23	91

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
12	HE2ES51	209745 4/07/98	Uni-ZAP XR	22	1447	1	1447	77	77	129	1	14	15	222
13	HAGGI80	209745 4/07/98	Uni-ZAP XR	23	3886	1289	3886	251	251	130	1	56	57	760
13	HAGGI80	209745 4/07/98	Uni-ZAP XR	108	1576	1	1576	40	40	215	1	34	35	84
14	HTXDW56	209746 4/07/98	Uni-ZAP XR	24	1583	1	1583	217	217	131	1	22	23	201
15	HEEAG23	209745 4/07/98	Uni-ZAP XR	25	1669	25	1280	57	57	132	1	18	19	46
16	HDPKI93	209745 4/07/98	pCMVSPORT 3.0	26	1053	1	1053	46	46	133	1	21	22	305
17	HDLAC10	209745 4/07/98	pCMVSPORT 2.0	27	1477	1	1477	132	132	134	1	29	30	81
18	HDPOH06	209745 4/07/98	pCMVSPORT 3.0	28	2504	1	2504	252	252	135	1	29	30	242
19	HCE4G61	209745 4/07/98	Uni-ZAP XR	29	1866	1	1866	130	130	136	1	23	24	285
19	HCE4G61	209745 4/07/98	Uni-ZAP XR	109	1779	1	1720	125	125	216	1	20	21	81
20	HCWU113	209745 4/07/98	ZAP Express	30	1501	1	1501	80	80	137	1	18	19	157

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
21	HDPSP01	209745 4/07/98	pCMVSPORT 3.0	31	1752	1	1752	227	227	138	1	20	21	308
22	HHPEN62	209746 4/07/98	Uni-ZAP XR	32	2152	141	2152	183	183	139	1	27	28	508
23	HUKBT29	209746 4/07/98	Lambda ZAP II	33	1757	56	1757	74	74	140	1	19	20	506
24	HMAJR50	209683 3/20/98	Uni-ZAP XR	34	1466	32	1466	70	70	141	1	21	22	48
25	HBIMB51	209683 3/20/98	pCMVSPORT 3.0	35	526	1	526	93	93	142	1	21	22	130
26	HE8DX88	209683 3/20/98	Uni-ZAP XR	36	2412	1	2412	256	256	143	1	29	30	43
27	HNGHT03	209746 4/07/98	Uni-ZAP XR	37	1274	65	1274	305	305	144	1	24	25	91
28	HWABU17	209745 4/07/98	pCMVSPORT 3.0	38	1036	1	1036	202	202	145	1	18	19	266
29	HDTAT90	209746 4/07/98	pCMVSPORT 2.0	39	1379	8	1379	78	78	146	1	26	27	434
30	HHFGR93	209746 4/07/98	Uni-ZAP XR	40	1932	1	1836	130	130	147	1	29	30	236
31	HOVCB25	209746 4/07/98	pSPORT1	41	1430	1	1430	150	150	148	1	18	19	99

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
32	HSYAV66	209746 4/07/98	pCMVSPORT 3.0	42	1407	1	1407	186	186	149	1	28	29	69
33	HFPCT29	209683 3/20/98	Uni-ZAP XR	43	950	1	950	268	268	150	1	26	27	61
34	HAWAT25	209683 3/20/98	pBluescript SK-	44	1004	56	1004	149	149	151	1	32	33	88
35	HNHFR04	209683 3/20/98	Uni-ZAP XR	45	1681	1	1681	71	71	152	1	21	22	78
36	HOSFT61	209683 3/20/98	Uni-ZAP XR	46	1361	1	1361	210	210	153	1	21	22	123
36	HOSFT61	209683 3/20/98	Uni-ZAP XR	110	1365	1	1365	211	211	217	1	21	22	90
37	HBJIO81	209683 3/20/98	Uni-ZAP XR	47	1137	1	1137	220	220	154	1	23	24	68
38	HADCL55	209745 4/07/98	pSPORT1	48	2763	15	2763	60	60	155	1	29	30	43
39	HAIBO81	209745 4/07/98	Uni-ZAP XR	49	1348	1	1348	250	250	156	1	18	19	63
40	HBBBC37	209745 4/07/98	pCMVSPORT 1	50	1264	1	1264	81	81	157	1	17	18	61
41	HBIMX85	209745 4/07/98	Uni-ZAP XR	51	1660	39	1660	45	45	158	1	18	19	82

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
42	HCEES66	209745 4/07/98	Uni-ZAP XR	52	1678	1	1678	178	178	159	1	39	40	46
43	HCEMP62	209745 4/07/98	Uni-ZAP XR	53	1860	269	1726	352	352	160	1	30	31	187
43	HCEMP62	209745 4/07/98	Uni-ZAP XR	111	1957	582	1823	19	19	218	1	33	34	335
44	HE2FB90	209746 4/07/98	Uni-ZAP XR	54	1663	1	1663	205	205	161	1	27	28	113
45	HTHDJ94	209746 4/07/98	Uni-ZAP XR	55	1632	20	1632	66	66	162	1	26	27	292
46	HTOHJ89	209746 4/07/98	Uni-ZAP XR	56	2233	1	2233	42	42	163	1	17	18	86
47	HUSHB62	209745 4/07/98	Lambda ZAP II	57	1963	1	1760	130	130	164	1	49	50	106
48	HSXAG02	209683 3/20/98	Uni-ZAP XR	58	1267	411	1243	600	600	165	1	22	23	58
49	HHTLH52	209683 3/20/98	ZAP Express	59	1295	1	1295	218	218	166	1	22	23	40
50	HCFMS95	209683 3/20/98	pSport1	60	915	1	915	123	123	167	1	22	23	65
51	HOUCT90	209683 3/20/98	Uni-ZAP XR	61	1445	1	1445	74	74	168	1	30	31	46



Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
52	HCFLR78	209745 4/07/98	pSport1	62	1100	224	1100	475	475	169	1	16	17	140
53	HTOHT18	209745 4/07/98	Uni-ZAP XR	63	1499	267	1499	433	433	170	1	24	25	53
54	HKPMB11	209745 4/07/98	pBluescript	64	655	1	655	55	55	171	1	25	26	167
54	HKPMB11	209745 4/07/98	pBluescript	112	1135	490	1135	350	350	219	1	30	31	229
55	HNHFS38	209745 4/07/98	Uni-ZAP XR	65	1450	1	1450	172	172	172	1	18	19	325
55	HNHFS38	209745 4/07/98	Uni-ZAP XR	113	1446	1	1446	171	171	220	1	18	19	62
56	HAIBU10	209745 4/07/98	Uni-ZAP XR	66	670	1	669	201	201	173	1	20	21	113
57	HAPOK30	209745 4/07/98	Uni-ZAP XR	67	1692	1	1692	300	300	174	1	19	20	61
58	HCEEM18	209745 4/07/98	Uni-ZAP XR	68	655	18	655	157	157	175	1	30	31	41
59	HCWUA22	209745 4/07/98	ZAP Express	69	1618	48	1618	233	233	176	1	33	34	42
60	HDSAG91	209745 4/07/98	Uni-ZAP XR	70	1802	1	1802	156	156	177	1	23	24	47

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
61	HNEDJ35	209746 4/07/98	Uni-ZAP XR	71	1292	1	1292	71	71	178	1	36	37	50
62	H7TBA62	209745 4/07/98	PCRII	72	883	1	807	199	199	179	1	65	66	227
62	H7TBA62	209745 4/07/98	PCRII	114	733	9	718	224	224	221	1	36	37	170
63	HNGIO50	209746 4/07/98	Uni-ZAP XR	73	785	1	785	132	132	180	1	27	28	44
64	HMIW81	209683 3/20/98	Uni-ZAP XR	74	2341	1	2215	229	229	181	1	17	18	46
65	HMMCJ60	209683 3/20/98	pSport1	75	1882	1	1882	132	132	182	1	16	17	41
66	HDPIO09	209745 4/07/98	pCMVSPORT 3.0	76	2892	17	2892	85	85	183	1	36	37	47
67	HHFHH34	209745 4/07/98	Uni-ZAP XR	77	1673	1	1673	16	16	184	1	22	23	70
68	HISCL83	209745 4/07/98	pSport1	78	1461	1	1461	259	259	185	1	21	22	41
69	HTOAI70	209746 4/07/98	Uni-ZAP XR	79	1517	1	1517	190	190	186	1	19	20	92
69	HTOAI70	209746 4/07/98	Uni-ZAP XR	115	1518	1	1518	190	190	222	1	19	20	42

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
70	HSDER95	209683 3/20/98	Uni-ZAP XR	80	574	1	574	72	72	187	1	25	26	71
71	HNECL25	209683 3/20/98	Uni-ZAP XR	81	1455	1	1455	322	322	188	1	32	33	66
72	HNFGZ45	209683 3/20/98	Uni-ZAP XR	82	1640	1	1640	450	450	189	1	38	39	70
73	HHGCU49	209745 4/07/98	Lambda ZAP II	83	525	1	525	173	173	190	1	23	24	40
74	HDPND68	209745 4/07/98	pCMVSPORT 3.0	84	837	1	837	154	154	191	1	17	18	66
75	HETDT81	209746 4/07/98	Uni-ZAP XR	85	1574	1	1574	189	189	192	1	25	26	66
76	HHLBA14	209746 4/07/98	pBluescript SK-	86	1628	353	1627	546	546	193	1	24	25	48
77	HLTBU43	209746 4/07/98	Uni-ZAP XR	87	1795	1	1795	198	198	194	1	19	20	66
78	HNTSJ84	209746 4/07/98	pSport1	88	1864	239	1864	336	336	195	1	22	23	57
79	HOHCG16	209746 4/07/98	pCMVSPORT 2.0	89	1983	1	1983	257	257	196	1	18	19	52
80	HTHCB31	209746 4/07/98	Uni-ZAP XR	90	1957	1	1957	46	46	197	1	17	18	43

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
81	HUKAM16	209746 4/07/98	Lambda ZAP II	91	573	1	573	178	178	198	1	23	24	52
82	HLDOJ66	209683 3/20/98	pCMVSPORT 3.0	92	1212	1	1212	313	313	199	1	20	21	40
83	HTXKF10	209683 3/20/98	Uni-ZAP XR	93	1144	1	1144	334	334	200	1	32	33	71
84	HPMAI22	209683 3/20/98	Uni-ZAP XR	94	1274	334	1274	483	483	201	1	16	17	59
85	HL2AG57	209746 4/07/98	Uni-ZAP XR	95	1780	349	1780	560	560	202	1	31	32	80
86	HTHBH29	209746 4/07/98	Uni-ZAP XR	96	1794	1223	1431	93	93	203	1	30	31	70
86	HTHBH29	209746 4/07/98	Uni-ZAP XR	116	1054	1	1054	52	52	223	1	24	25	56
87	HUSAM59	209683 3/20/98	Lambda ZAP II	97	2065	1	2065	475	475	204	1	17	18	78
88	HNGGR26	209745 4/07/98	Uni-ZAP XR	98	1154	1	1154	50	50	205	1	27	28	115
89	HTLCX30	209683 3/20/98	Uni-ZAP XR	99	615	1	459	60	60	206	1	28	29	50
90	HCEBC87	209683 3/20/98	Uni-ZAP XR	100	1624	243	1624	517	517	207	1	23	24	57

Gene No.	cDNA Clone ID	ATCC Deposit Nr and Date	Vector	NT SEQ ID NO: X	Total NT Seq.	5' NT of Clone Seq.	3' NT of Clone Seq.	5' NT of Start Codon	5' NT of First AA of Signal Pep	AA SEQ ID NO: Y	First AA of Sig Pep	Last AA of Sig Pep	First AA of Secreted Portion	Last AA of ORF
91	HATCB92	209683 3/20/98	Uni-ZAP XR	101	1756	1	1756	247	247	208	1	40	41	56
92	HMSCX69	209746 4/07/98	Uni-ZAP XR	102	1416	207	1416	246	246	209	1	16	17	49
93	HLHAL68	209746 4/07/98	Uni-ZAP XR	103	704	1	704	30	30	210	1	21	22	44
94	HEOMR73	209746 4/07/98	pSport1	104	1259	644	1259	354	354	211	1	24	25	44
95	HETIB83	209746 4/07/98	Uni-ZAP XR	105	1804	1	1804	104	104	212	1	30	31	160
96	HJPDD28	209746 4/07/98	Uni-ZAP XR	106	971	260	971	283	283	213	1	21	22	198
96	HJPDD28	209746 4/07/98	Uni-ZAP XR	117	921	1	921	31	31	224	1	21	22	96
97	HBAMB15	209683 3/20/98	pSport1	107	821	330	821	390	390	214	1	19	20	59

Table 1 summarizes the information corresponding to each “Gene No.” described above. The nucleotide sequence identified as “NT SEQ ID NO:X” was assembled from partially homologous (“overlapping”) sequences obtained from the “cDNA clone ID” identified in Table 1 and, in some cases, from additional related DNA clones. The overlapping sequences were assembled into a single contiguous sequence of high redundancy (usually three to five overlapping sequences at each nucleotide position), resulting in a final sequence identified as SEQ ID NO:X.

[0688] The cDNA Clone ID was deposited on the date and given the corresponding deposit number listed in “ATCC Deposit No:Z and Date.” Some of the deposits contain multiple different clones corresponding to the same gene. “Vector” refers to the type of vector contained in the cDNA Clone ID.

[0689] “Total NT Seq.” refers to the total number of nucleotides in the contig identified by “Gene No.” The deposited clone may contain all or most of these sequences, reflected by the nucleotide position indicated as “5’ NT of Clone Seq.” and the “3’ NT of Clone Seq.” of SEQ ID NO:X. The nucleotide position of SEQ ID NO:X of the putative start codon (methionine) is identified as “5’ NT of Start Codon.” Similarly, the nucleotide position of SEQ ID NO:X of the predicted signal sequence is identified as “5’ NT of First AA of Signal Pep.”

[0690] The translated amino acid sequence, beginning with the methionine, is identified as “AA SEQ ID NO:Y,” although other reading frames can also be easily translated using known molecular biology techniques. The polypeptides produced by these alternative open reading frames are specifically contemplated by the present invention.

[0691] The first and last amino acid position of SEQ ID NO:Y of the predicted signal peptide is identified as “First AA of Sig Pep” and “Last AA of Sig Pep.” The predicted first amino acid position of SEQ ID NO:Y of the secreted portion is identified as “Predicted First AA of Secreted Portion.” Finally, the amino acid position of SEQ ID NO:Y of the last amino acid in the open reading frame is identified as “Last AA of ORF.”

[0692] SEQ ID NO:X (where X may be any of the polynucleotide sequences disclosed in the sequence listing) and the translated SEQ ID NO:Y (where Y may be

any of the polypeptide sequences disclosed in the sequence listing) are sufficiently accurate and otherwise suitable for a variety of uses well known in the art and described further below. For instance, SEQ ID NO:X is useful for designing nucleic acid hybridization probes that will detect nucleic acid sequences contained in SEQ ID NO:X or the cDNA contained in the deposited clone. These probes will also hybridize to nucleic acid molecules in biological samples, thereby enabling a variety of forensic and diagnostic methods of the invention. Similarly, polypeptides identified from SEQ ID NO:Y may be used, for example, to generate antibodies which bind specifically to proteins containing the polypeptides and the secreted proteins encoded by the cDNA clones identified in Table 1.

[0693] Nevertheless, DNA sequences generated by sequencing reactions can contain sequencing errors. The errors exist as misidentified nucleotides, or as insertions or deletions of nucleotides in the generated DNA sequence. The erroneously inserted or deleted nucleotides cause frame shifts in the reading frames of the predicted amino acid sequence. In these cases, the predicted amino acid sequence diverges from the actual amino acid sequence, even though the generated DNA sequence may be greater than 99.9% identical to the actual DNA sequence (for example, one base insertion or deletion in an open reading frame of over 1000 bases).

[0694] Accordingly, for those applications requiring precision in the nucleotide sequence or the amino acid sequence, the present invention provides not only the generated nucleotide sequence identified as SEQ ID NO:X and the predicted translated amino acid sequence identified as SEQ ID NO:Y, but also a sample of plasmid DNA containing a human cDNA of the invention deposited with the ATCC, as set forth in Table 1. The nucleotide sequence of each deposited clone can readily be determined by sequencing the deposited clone in accordance with known methods. The predicted amino acid sequence can then be verified from such deposits. Moreover, the amino acid sequence of the protein encoded by a particular clone can also be directly determined by peptide sequencing or by expressing the protein in a suitable host cell containing the deposited human cDNA, collecting the protein, and determining its sequence.

**[0695]** The present invention also relates to the genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, or the deposited clone. The corresponding gene can be isolated in accordance with known methods using the sequence information disclosed herein. Such methods include preparing probes or primers from the disclosed sequence and identifying or amplifying the corresponding gene from appropriate sources of genomic material.

**[0696]** Also provided in the present invention are allelic variants, orthologs, and/or species homologs. Procedures known in the art can be used to obtain full-length genes, allelic variants, splice variants, full-length coding portions, orthologs, and/or species homologs of genes corresponding to SEQ ID NO:X, SEQ ID NO:Y, or a deposited clone, using information from the sequences disclosed herein or the clones deposited with the ATCC. For example, allelic variants and/or species homologs may be isolated and identified by making suitable probes or primers from the sequences provided herein and screening a suitable nucleic acid source for allelic variants and/or the desired homologue.

**[0697]** Table 2 summarizes the expression profile of polynucleotides corresponding to the clones disclosed in Table 1. The first column provides a unique clone identifier, "Clone ID", for a cDNA clone related to each contig sequence disclosed in Table 1. Column 2, "Library Code" shows the expression profile of tissue and/or cell line libraries which express the polynucleotides of the invention. Each Library Code in column 2 represents a tissue/cell source identifier code corresponding to the Library Code and Library description provided in Table 4. Expression of these polynucleotides was not observed in the other tissues and/or cell libraries tested. One of skill in the art could routinely use this information to identify tissues which show a predominant expression pattern of the corresponding polynucleotide of the invention or to identify polynucleotides which show predominant and/or specific tissue expression.

**[0698]** Table 3, column 1, provides a nucleotide sequence identifier, "SEQ ID NO:X," that matches a nucleotide SEQ ID NO:X disclosed in Table 1, column 5. Table 3, column 2, provides the chromosomal location, "Cytologic Band or Chromosome," of polynucleotides corresponding to SEQ ID NO:X. Chromosomal



location was determined by finding exact matches to EST and cDNA sequences contained in the NCBI (National Center for Biotechnology Information) UniGene database. Given a presumptive chromosomal location, disease locus association was determined by comparison with the Morbid Map, derived from Online Mendelian Inheritance in Man (Online Mendelian Inheritance in Man, OMIM™. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine (Bethesda, MD) 2000. World Wide Web URL: <http://www.ncbi.nlm.nih.gov/omim/>). If the putative chromosomal location of the Query overlapped with the chromosomal location of a Morbid Map entry, the OMIM reference identification number of the morbid map entry is provided in Table 3, column 3, labelled "OMIM ID." A key to the OMIM reference identification numbers is provided in Table 5.

**[0699]** Table 4 provides a key to the Library Code disclosed in Table 2. Column 1 provides the Library Code disclosed in Table 2, column 2. Column 2 provides a description of the tissue or cell source from which the corresponding library was derived.

**[0700]** Table 5 provides a key to the OMIM reference identification numbers disclosed in Table 3, column 3. OMIM reference identification numbers (Column 1) were derived from Online Mendelian Inheritance in Man (Online Mendelian Inheritance in Man, OMIM. McKusick-Nathans Institute for Genetic Medicine, Johns Hopkins University (Baltimore, MD) and National Center for Biotechnology Information, National Library of Medicine, (Bethesda, MD) 2000. World Wide Web URL: <http://www.ncbi.nlm.nih.gov/omim/>). Column 2 provides diseases associated with the cytologic band disclosed in Table 3, column 2, as determined using the Morbid Map database.

**Table 2**

Clone ID	Library Codes
HKABZ65	H0494
HNGIC80	S0052
HDPUG50	H0013 H0038 H0046 H0083 H0144 H0212 H0438 H0457 H0488 H0494 H0497 H0521 H0543 H0545 H0580 H0581 H0583 H0591 H0597 H0599 H0616 H0627 H0659 H0661 H0665 H0672 H0673 H0674 H0682 H0685 L0055 L0163 L0362 L0517 L0545 L0659 L0662 L0740 L0747 L0748 L0758 L0759 L0763 L0766 L0767 L0770 L0771 L0776 L0777 L0779 L0782 S0010 S0026 S0142 S0214 S0344 S0360 S0390 S0420 S0434
HAEAB66	H0266 H0494 H0646 H0676 L0383 L0517 L0596 L0659 L0662 L0747 L0748 L0749 L0750 L0752 L0755 L0758 L0761 L0764 L0771 L0774 L0777 L0783 L0789 L0792 L0800 L0803 L0804 L0806 L0809 S0116 S0356 S0358 S0402 T0048 T0109
HHEPF59	H0038 H0063 H0254 H0255 H0264 H0318 H0333 H0389 H0392 H0413 H0422 H0428 H0445 H0449 H0483 H0521 H0542 H0543 H0556 H0583 H0606 H0615 H0648 H0664 H0673 H0702 L0157 L0382 L0439 L0447 L0471 L0595 L0646 L0650 L0655 L0659 L0662 L0665 L0666 L0748 L0756 L0761 L0764 L0766 L0768 L0769 L0779 L0782 L0789 L0791 L0803 L0809 S0027 S0028 S0049 S0212 S0418
HE9BK23	H0014 H0098 H0144 H0355 H0393 H0509 H0510 H0574 H0632 L0581 L0748 L0775 L0790 L0803 L0804
HCYBI36	H0014 H0031 H0123 H0156 H0170 H0171 H0188 H0264 H0295 H0341 H0428 H0431 H0435 H0445 H0479 H0494 H0509 H0520 H0521 H0529 H0530 H0543 H0547 H0551 H0574 H0575 H0586 H0587 H0592 H0596 H0620 H0633 H0638 H0648 H0658 H0661 H0670 H0672 H0674 H0684 H0690 L0021 L0157 L0362 L0448 L0451 L0483 L0525 L0589 L0602 L0637 L0646 L0648 L0649 L0653 L0655 L0657 L0662 L0664 L0665 L0717 L0731 L0740 L0747 L0748 L0749 L0752 L0754 L0755 L0758 L0759 L0761 L0763 L0764 L0766 L0770 L0774 L0775 L0776 L0777 L0779 L0780 L0803 L0804 L0806 L0809 S0003 S0014 S0052 S0122 S0132 S0194 S0212 S0242 S0352 S0358 S0374 S0378 S0388 S0422 S0450 S3014 T0002 T0010 T0023 T0040 T0114
HSSDX51	H0050 H0052 H0069 H0135 H0391 H0575 H0652 H0690 L0021 L0438 L0439 L0554 L0599 L0653 L0665 L0717 L0774 L0775 S0038 S0049 S0222 S0312 S0334 S0338 T0006 T0082
HSDAJ46	H0009 H0052 H0144 H0352 H0392 L0593 L0595 L0598 L0608 L0740 L0741 L0745 L0746 L0748 L0749 L0759 L0769 L0770 L0777 L0783 L0809 S0031
HRACG45	H0009 H0030 H0036 H0059 H0555 L0599 S0358
HAPPW30	H0009 H0012 H0038 H0052 H0103 H0135 H0169 H0188 H0208 H0213 H0266 H0292 H0388 H0412 H0424 H0521 H0538 H0539 H0545 H0547 H0575 H0616 H0653 H0663 H0672 L0163 L0591 L0599 L0638 L0665 L0731 L0742 L0747 L0748 L0752 L0753 L0755 L0757 L0758 L0759 L0764 L0767 L0769 L0770 L0772 L0774 L0775 L0776 L0777 L0779 L0786 L0809 S0010 S0027 S0045 S0049 S0392 S0474 T0040 T0041 T0042
HE2ES51	H0015 H0038 H0170 H0356 H0622 L0774 L0803 S0015 S0438
HAGGJ80	H0040 H0144 H0327 H0422 H0427 H0539 H0542 H0547 H0551 H0561 H0581 H0648 H0658 H0659 H0672 H0684 L0157 L0352 L0362 L0438 L0471 L0519 L0591 L0659 L0662 L0663 L0665 L0731 L0756 L0758 L0759 L0764 L0766 L0774 L0775 L0777 L0779 L0783 S0003 S0028

	S0036 S0051 S0150 S0152 S0342 S0346 S0358 S0360 S0374
HTXDW56	H0009 H0024 H0031 H0038 H0039 H0040 H0042 H0046 H0051 H0061 H0069 H0083 H0100 H0123 H0144 H0156 H0208 H0251 H0264 H0265 H0266 H0271 H0295 H0327 H0351 H0370 H0393 H0427 H0431 H0435 H0436 H0457 H0484 H0485 H0494 H0519 H0521 H0522 H0529 H0542 H0543 H0545 H0547 H0551 H0556 H0561 H0580 H0581 H0586 H0616 H0617 H0622 H0624 H0635 H0642 H0644 H0656 H0658 H0660 H0661 H0667 H0687 H0688 H0696 L0021 L0040 L0373 L0439 L0515 L0565 L0591 L0595 L0596 L0598 L0605 L0626 L0636 L0637 L0638 L0653 L0655 L0659 L0662 L0663 L0664 L0665 L0666 L0731 L0740 L0742 L0744 L0745 L0747 L0748 L0749 L0750 L0751 L0752 L0754 L0755 L0756 L0757 L0758 L0759 L0761 L0763 L0764 L0766 L0770 L0771 L0776 L0789 L0794 L0803 L0804 L0805 L0806 L0809 S0002 S0003 S0010 S0026 S0027 S0040 S0042 S0044 S0045 S0114 S0116 S0132 S0134 S0192 S0212 S0278 S0316 S0328 S0330 S0356 S0358 S0360 S0374 S0376 S0378 S0380 S0412 S0414 S0426 S0462 S0474 T0082
HEEAG23	H0038 H0052 H0123 H0144 H0194 H0255 H0286 H0328 H0375 H0436 H0484 H0521 H0542 H0549 H0556 H0624 L0748 L0789 S0027 S0030 S0126 S0196 S0222 S0278 S0300 S0358 S0420
HDPKI93	H0024 H0039 H0052 H0059 H0087 H0135 H0144 H0255 H0264 H0265 H0295 H0341 H0393 H0478 H0494 H0510 H0521 H0522 H0539 H0543 H0549 H0574 H0597 H0598 H0616 H0677 L0565 L0588 L0596 L0665 L0738 L0743 L0747 L0749 L0751 L0769 S0126 S0146 S0206 S0210 S0356 S0360
HDLAC10	H0031 H0170 H0320 H0373 H0422 H0445 H0485 H0494 H0519 H0539 H0543 H0550 H0555 H0581 H0586 H0650 H0657 H0658 H0672 H0690 L0374 L0438 L0599 L0606 L0635 L0638 L0655 L0665 L0666 L0667 L0743 L0745 L0759 L0761 L0764 L0766 L0777 L0779 L0803 L0804 S0134 S0212 S0218 S0358 S0360 T0067
HDPOH06	H0046 H0087 H0318 H0431 H0521 H0522 L0599 L0608 L0662 L0663 L0666 L0731 L0748 L0749 L0774 L0775 L0777 L0783 L0803 S0318 S0344
HCWUI13	H0589
HDPSP01	H0052 H0059 H0100 H0123 H0135 H0370 H0392 H0427 H0478 H0494 H0521 H0545 H0550 H0551 H0555 H0586 H0617 H0618 H0620 H0684 L0665 L0666 L0731 L0743 L0745 L0747 L0750 L0751 L0752 L0755 L0759 L0764 L0769 L0771 L0774 L0775 L0777 L0780 L0783 L0792 L0804 L0805 L0806 L0809 S0051 S0132 S0314 S0328 S0418 S3014
HHPEN62	H0046 H0051 H0052 H0100 H0261 H0305 H0327 H0438 L0635 L0741 L0769 L0770 L0803 S0010 S0036 S0051 S0112 S0260 S0282 S0346
HUKBT29	H0002 H0051 H0059 H0116 H0149 H0255 H0522 H0543 H0555 H0599 L0366 L0460 L0485 L0604 L0747 L0777 L0803 S0330 S0364 S0366 S0428 S0430 S0446
HMAJR50	H0013 H0014 H0031 H0032 H0038 H0040 H0046 H0051 H0052 H0056 H0059 H0069 H0090 H0123 H0130 H0134 H0144 H0170 H0250 H0267 H0316 H0327 H0328 H0341 H0357 H0402 H0412 H0416 H0421 H0423 H0436 H0441 H0445 H0497 H0519 H0520 H0521 H0529 H0542 H0543 H0546 H0547 H0549 H0551 H0553 H0556 H0560 H0574 H0587 H0598 H0615 H0619 H0623 H0625 H0632 H0638 H0640 H0641 H0644 H0650 H0657 H0695 L0387 L0438 L0439 L0471 L0586 L0588 L0593 L0598 L0607 L0637 L0642 L0646 L0648 L0655 L0659 L0662 L0663 L0664 L0665 L0666 L0667 L0731 L0738 L0740 L0747 L0748 L0750 L0752

	L0754 L0755 L0756 L0757 L0758 L0759 L0767 L0770 L0771 L0775 L0776 L0779 L0806 S0003 S0013 S0026 S0028 S0036 S0053 S0116 S0126 S0132 S0144 S0152 S0196 S0210 S0222 S0260 S0278 S0348 S0352 S0354 S0356 S0358 S0360 S0374 S0378 S0380 S0418 S0452 S0474 T0006 T0082
HBIMB51	H0593 S0152
HE8DX88	H0013
HNGHT03	S0052
HWABU17	H0024 H0052 H0208 H0422 H0457 H0581 H0624 S0002 S0031 S0344 S0360 S0364 T0041
HDTAT90	H0052 H0224 H0252 H0280 H0486 H0539 H0592 H0616 S0045 S0150
HHFGR93	H0024 H0030 H0040 H0042 H0046 H0050 H0051 H0056 H0124 H0144 H0265 H0305 H0328 H0361 H0413 H0422 H0427 H0441 H0485 H0506 H0519 H0543 H0553 H0555 H0556 H0569 H0575 H0586 H0599 H0616 H0619 H0644 L0363 L0471 L0599 L0603 L0605 L0644 L0659 L0662 L0665 L0666 L0731 L0747 L0748 L0749 L0750 L0751 L0754 L0755 L0764 L0769 L0770 L0775 L0779 L0783 L0794 L0800 L0803 L0804 L0806 S0038 S0045 S0046 S0146 S0280 S0358 S3012
HOVCB25	H0428
HSYAV66	H0036 H0551
HFPCT29	S0222
HAWAT25	H0100 H0135 H0171 H0263 H0670 L0774 L0803 S0216 T0060
HNHFR04	S0053 S0428
HOSFT61	H0170 H0328 H0331 H0428 H0519 H0521 H0529 H0542 H0546 H0576 H0583 H0587 H0601 H0615 H0624 H0658 H0660 H0683 L0367 L0438 L0439 L0471 L0731 L0754 L0759 L0791 S0003 S0026 S0114 S0194 S0212 S0214 S0222 S0420 T0041
HBJIO81	H0318 L0766
HADCL55	H0013 H0031 H0038 H0144 H0253 H0266 H0310 H0424 H0427 H0497 H0519 H0521 H0522 H0539 H0545 H0549 H0553 H0555 H0581 H0591 H0599 H0618 H0633 H0661 H0664 L0021 L0142 L0438 L0439 L0649 L0659 L0662 L0664 L0665 L0740 L0745 L0747 L0748 L0758 L0759 L0769 L0779 L0790 S0010 S0126 S0144 S0218 S0360 S0390 S0418 S0422 S0426 S0452 S3014
HAIBO81	S0001 S0132
HBBBC37	H0013 H0014 H0038 H0069 H0096 H0100 H0201 H0264 H0374 H0486 H0494 H0543 H0551 H0587 H0687 L0021 L0105 L0369 L0438 L0439 L0471 L0485 L0591 L0598 L0599 L0659 L0717 L0740 L0743 L0748 L0749 L0751 L0752 L0755 L0756 L0758 L0768 L0769 L0770 L0771 L0774 L0775 L0776 L0777 L0779 L0792 L0794 L0803 L0804 L0805 L0806 S0001 S0003 S0122 S0222 S0260 S0330 S0346 S0388 S0468 T0023 T0039 T0042
HBJMX85	H0254 H0255 H0306 H0318 H0327 H0402 H0421 H0436 H0445 H0457 H0486 H0506 H0543 H0555 H0556 H0583 S0007 S0114 S0140 S0218 S0348 S0358
HCEES66	H0052 L0753 L0756
HCEMP62	H0024 H0030 H0040 H0041 H0046 H0052 H0063 H0123 H0135 H0165 H0179 H0181 H0188 H0208 H0264 H0266 H0286 H0290 H0318 H0370 H0402 H0411 H0428 H0436 H0445 H0484 H0489 H0506 H0509 H0521 H0522 H0543 H0547 H0551 H0553 H0556 H0561 H0575 H0581 H0583 H0586 H0587 H0593 H0596 H0600 H0617 H0620 H0622 H0667 H0668 H0672 H0702 H0707 L0372 L0517 L0521 L0565 L0599 L0637 L0657 L0662 L0663 L0664 L0665 L0666 L0717 L0731 L0744 L0747 L0748

	L0749 L0751 L0754 L0757 L0759 L0761 L0763 L0764 L0766 L0768 L0769 L0770 L0776 L0777 L0803 S0001 S0002 S0037 S0044 S0049 S0150 S0212 S0216 S0250 S0278 S0354 S0358 S0360 S0364 S0380 S0426 S0446 S0458 S3012 T0039
HE2FB90	H0012 H0050 H0130 H0171 H0318 H0333 H0428 H0539 H0549 H0571 H0624 H0662 L0439 L0639 L0665 L0750 L0755 L0756 L0764 L0769 L0772 L0792 L0794 S0046
HTHDJ94	H0009 H0013 H0039 H0042 H0046 H0052 H0063 H0123 H0124 H0135 H0144 H0150 H0156 H0163 H0170 H0200 H0264 H0295 H0423 H0445 H0486 H0494 H0519 H0520 H0521 H0543 H0544 H0545 H0553 H0556 H0561 H0575 H0581 H0593 H0599 H0600 H0606 H0644 H0645 H0652 H0658 H0662 H0673 H0674 L0005 L0055 L0143 L0369 L0438 L0439 L0485 L0519 L0520 L0526 L0536 L0549 L0637 L0659 L0731 L0740 L0748 L0750 L0752 L0753 L0755 L0757 L0758 L0759 L0763 L0764 L0766 L0768 L0770 L0774 L0776 L0777 L0779 L0783 L0803 L0806 L0809 S0002 S0010 S0027 S0032 S0132 S0358 S0364 S0434 S0466 S0474 S3012
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HUSHB62	H0012 H0013 H0030 H0031 H0032 H0038 H0039 H0044 H0046 H0052 H0056 H0059 H0070 H0083 H0090 H0100 H0122 H0123 H0124 H0134 H0135 H0144 H0150 H0156 H0194 H0201 H0220 H0231 H0253 H0255 H0261 H0264 H0266 H0271 H0306 H0351 H0352 H0356 H0370 H0375 H0393 H0402 H0412 H0413 H0422 H0423 H0424 H0427 H0429 H0431 H0435 H0436 H0437 H0438 H0441 H0445 H0478 H0483 H0484 H0486 H0494 H0506 H0510 H0518 H0521 H0529 H0539 H0542 H0543 H0545 H0549 H0551 H0553 H0555 H0556 H0561 H0575 H0580 H0581 H0583 H0586 H0587 H0591 H0593 H0599 H0615 H0616 H0617 H0618 H0620 H0622 H0623 H0626 H0634 H0635 H0641 H0644 H0646 H0650 H0656 H0657 H0661 H0662 H0664 H0665 H0670 H0672 H0673 H0679 H0682 H0685 H0687 H0691 H0696 H0702 H0707 L0041 L0142 L0143 L0157 L0352 L0362 L0372 L0375 L0378 L0388 L0438 L0439 L0493 L0498 L0511 L0515 L0517 L0518 L0529 L0540 L0553 L0560 L0564 L0596 L0599 L0600 L0603 L0608 L0612 L0635 L0638 L0641 L0644 L0645 L0646 L0650 L0651 L0656 L0657 L0658 L0659 L0662 L0663 L0664 L0665 L0666 L0667 L0697 L0731 L0740 L0741 L0742 L0743 L0744 L0745 L0747 L0748 L0749 L0750 L0751 L0752 L0754 L0758 L0759 L0761 L0762 L0763 L0766 L0767 L0768 L0769 L0770 L0771 L0774 L0775 L0777 L0779 L0783 L0786 L0789 L0791 L0794 L0796 L0803 L0804 L0806 L0809 S0007 S0010 S0011 S0027 S0028 S0031 S0032 S0037 S0038 S0040 S0045 S0046 S0049 S0053 S0116 S0126 S0132 S0140 S0144 S0192 S0194 S0212 S0222 S0260 S0278 S0280 S0282 S0350 S0354 S0356 S0358 S0360 S0376 S0378 S0384 S0390 S0418 S0426 S0428 S3012 S3014 S6024 T0002 T0049 T0067
HSXAG02	H0013 H0014 H0024 H0031 H0032 H0038 H0039 H0040 H0046 H0050 H0051 H0052 H0056 H0057 H0081 H0085 H0086 H0087 H0100 H0105 H0116 H0123 H0124 H0135 H0144 H0150 H0163 H0171 H0178 H0181 H0188 H0196 H0208 H0242 H0251 H0252 H0253 H0264 H0266 H0268 H0269 H0274 H0284 H0286 H0290 H0292 H0294 H0309 H0316 H0318 H0333 H0343 H0352 H0381 H0392 H0411 H0412 H0413 H0427 H0428 H0437 H0484 H0485 H0486 H0506 H0519 H0520 H0539 H0544 H0545 H0546 H0547 H0549 H0550 H0551 H0553 H0575 H0586 H0587 H0590 H0592 H0594 H0597 H0598 H0599 H0600 H0602 H0617 H0619 H0620 H0622 H0623 H0624 H0626 H0628 H0631 H0647 H0648 H0653 H0659 H0660 H0664 H0665 H0667 H0673 H0677 H0684 H0687 H0688 H0689 H0690 H0691 H0696 L0005 L0021 L0053 L0361 L0364 L0372 L0375

	L0378 L0384 L0426 L0438 L0439 L0471 L0493 L0517 L0521 L0523 L0542 L0565 L0588 L0592 L0596 L0597 L0598 L0629 L0637 L0645 L0646 L0648 L0649 L0651 L0653 L0654 L0656 L0657 L0659 L0662 L0663 L0664 L0665 L0666 L0717 L0731 L0740 L0742 L0743 L0744 L0747 L0748 L0749 L0750 L0751 L0754 L0755 L0757 L0758 L0759 L0762 L0763 L0764 L0768 L0769 L0770 L0771 L0772 L0774 L0775 L0776 L0777 L0779 L0780 L0783 L0796 L0800 L0803 L0806 L0807 S0001 S0011 S0022 S0026 S0027 S0028 S0036 S0037 S0038 S0040 S0044 S0045 S0046 S0116 S0126 S0192 S0194 S0196 S0208 S0210 S0212 S0242 S0250 S0294 S0328 S0330 S0332 S0342 S0352 S0354 S0356 S0358 S0360 S0364 S0374 S0376 S0388 S0418 S0420 S0432 S0446 S0312 S0314 T0003 T0004 T0040 T0049
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HOUCT90	S0040
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HKPMB11	H0453 H0575 L0803 S0126 S0210
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HAIBU10	H0087 H0135 H0166 H0171 H0188 H0213 H0252 H0263 H0333 H0343 H0427 H0457 H0545 H0556 H0580 H0587 H0594 H0624 H0634 H0660 H0666 H0674 H0689 L0021 L0471 L0615 L0637 L0644 L0653 L0659 L0663 L0665 L0717 L0731 L0743 L0748 L0750 L0753 L0754 L0757 L0758 L0759 L0761 L0762 L0763 L0764 L0766 L0769 L0770 L0775 L0776 L0779 L0790 L0791 L0794 L0800 L0803 L0804 L0805 L0809 S0013 S0116 S0132 S0134 S0144 S0354 S0358 S0450

HAPOK30	H0575 H0592 H0670 L0352 L0439 L0517 L0600 L0608 L0663 L0740 L0747 L0752 L0755 L0756 L0759 L0763 L0764 L0766 L0768 L0770 L0777 L0785 L0794 L0803 L0809 S0010 S0222 S0328
HCEEM18	H0012 H0014 H0023 H0024 H0031 H0036 H0051 H0052 H0069 H0081 H0111 H0123 H0124 H0179 H0253 H0266 H0271 H0294 H0305 H0309 H0327 H0333 H0341 H0370 H0429 H0449 H0486 H0494 H0506 H0510 H0521 H0539 H0543 H0544 H0550 H0551 H0575 H0581 H0586 H0599 H0616 H0620 H0623 H0628 H0635 H0644 H0653 H0657 H0665 H0683 L0382 L0471 L0565 L0601 L0604 L0651 L0664 L0745 L0750 L0752 L0754 L0757 L0758 L0759 L0766 L0769 L0779 L0789 L0794 L0800 L0803 S0002 S0022 S0027 S0028 S0037 S0040 S0044 S0045 S0046 S0051 S0126 S0142 S0144 S0152 S0212 S0220 S0278 S0344 S0356 S0358 S0360 S0420 S0424 S3014 T0010 T0040 T0041 T0042 T0049
HCWUA22	H0305 H0589
HDSAG91	H0329 H0635 L0766
HNEDJ35	H0179 H0435
H7TBA62	S0198 S0228 S0252 S0264 S0268 S0270 S0274
HNGIO50	S0052
HMLAW81	H0046 H0328 H0445 L0519 S6028
HMMCJ60	H0124 H0444 S0053
HDPIO09	H0006 H0013 H0014 H0031 H0032 H0039 H0040 H0051 H0052 H0059 H0090 H0196 H0252 H0265 H0266 H0294 H0309 H0328 H0373 H0375 H0421 H0422 H0423 H0427 H0428 H0431 H0445 H0486 H0488 H0497 H0510 H0521 H0529 H0542 H0547 H0550 H0553 H0556 H0561 H0574 H0580 H0591 H0596 H0622 H0623 H0624 H0628 H0634 H0637 H0641 H0644 H0648 H0658 H0659 H0661 H0676 H0684 H0687 L0439 L0481 L0485 L0512 L0517 L0563 L0638 L0646 L0651 L0659 L0661 L0662 L0663 L0664 L0665 L0666 L0682 L0697 L0731 L0740 L0745 L0747 L0748 L0749 L0750 L0751 L0752 L0754 L0755 L0756 L0757 L0758 L0759 L0763 L0764 L0766 L0768 L0769 L0770 L0774 L0775 L0776 L0777 L0779 L0780 L0783 L0789 L0809 S0001 S0002 S0003 S0010 S0027 S0028 S0038 S0046 S0051 S0114 S0116 S0142 S0218 S0222 S0276 S0294 S0328 S0330 S0346 S0354 S0356 S0374 T0042
HHFHH34	H0050 H0520
HISCL83	H0539
HTOAI70	H0264
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HNECL25	H0179
HNFGZ45	H0179 H0264 H0271 H0422 H0619 S0358
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HDPND68	H0063 H0144 H0264 H0305 H0316 H0402 H0427 H0431 H0517 H0522 H0690 L0021 L0378 L0381 L0527 L0534 L0539 L0562 L0589 L0665 L0745 L0748 L0751 L0766 L0770 S0001 S0002 S0038 S0052
HETDT81	H0038 H0046 H0090 H0253 H0539 H0617 L0439 L0455 L0646 L0649 L0658 L0659 L0662 L0750 L0754 L0764 L0766 L0771 L0777 L0780 L0789 L0803 S0142 S0344 S0358
HHLBA14	H0013 H0264 H0427 H0547 L0438 L0439 S0010 S0222 T0041 T0091

HLTBU43	H0090
HNTSJ84	H0013 H0428 H0542 H0547 H0622 L0636 L0662 L0717 L0740 L0749 L0766 L0769 L0779 L0789 S0007 S0242 S0282 S0354
HOHCG16	H0411 H0509 H0538 L0439 L0532 L0743 L0744 L0748 L0749 S0250
HTHCB31	H0063 H0170 L0589 S0001
HUKAM16	H0028 H0059 H0081 H0135 H0194 H0231 H0255 H0264 H0352 H0423 H0483 H0521 H0529 H0542 H0547 H0553 H0587 H0616 H0628 H0662 H0663 H0687 L0439 L0471 L0526 L0605 L0639 L0664 L0665 L0743 L0744 L0745 L0747 L0748 L0759 L0769 L0774 L0776 L0777 L0809 S0002 S0007 S0036 S0212 S0330 S0360 S0378 S0418 S0428 T0010
HLDOJ66	H0510
HTXKF10	H0556
HPMAI22	H0031 H0662 L0600 L0657 L0755 L0756 L0767 L0768 L0779 L0794
HL2AG57	H0013 H0090 H0131 H0135 H0264 H0341 H0359 H0519 H0689 L0439 L0637 L0640 L0647 L0659 L0665 L0764 L0768 L0779 S0212
HTHBH29	H0063 H0100 H0520
HUSAM59	H0032 H0052 H0068 H0083 H0090 H0156 H0170 H0171 H0212 H0266 H0268 H0309 H0392 H0411 H0422 H0423 H0435 H0441 H0445 H0494 H0519 H0529 H0543 H0547 H0561 H0574 H0591 H0596 H0628 H0633 H0656 H0657 H0658 H0667 H0686 H0696 L0438 L0439 L0471 L0519 L0521 L0581 L0598 L0601 L0649 L0653 L0659 L0662 L0664 L0665 L0666 L0717 L0740 L0742 L0745 L0747 L0750 L0752 L0753 L0754 L0755 L0756 L0758 L0764 L0766 L0768 L0770 L0773 L0775 L0777 L0779 L0780 L0782 L0783 L0789 L0794 L0803 L0804 L0809 S0011 S0022 S0042 S0051 S0192 S0242 S0358 S0360 S0374 S0380 S0402 S0424 S0474 S6028 T0069 T0114
HNGGR26	S0052
HTLCX30	H0253 L0758 L0794
HCEBC87	H0052 H0163 H0171 H0351 H0411 H0415 H0592 H0694 L0439 L0465 L0520 L0592 L0650 L0657 L0666 L0745 L0748 L0751 L0752 L0755 L0756 L0758 L0766 L0777 L0779 L0783 L0788 L0803 L0805 S0010 S0136 S0358
HATCB92	H0156
HMSCX69	H0063 H0100 H0139 H0144 H0264 H0318 H0327 H0331 H0538 H0650 H0656 L0381 L0438 L0606 L0638 L0740 L0749 L0750 L0754 L0756 L0759 L0761 L0766 L0769 L0770 L0774 L0777 L0779 L0792 S0002 S0053 T0010
HLHAL68	H0024
HEOMR73	H0179 H0271 H0457 H0695 L0748
HETIB83	H0046 H0134 H0306 H0318 H0396 H0402 H0429 H0445 H0560 H0581 H0638 H0650 H0656 H0657 H0689 L0438 L0439 L0655 L0740 L0761 L0766 L0777 L0789 L0794 S0002 S0038 S0050 S0278 S0344
HJPDD28	H0002 H0014 H0015 H0024 H0031 H0036 H0040 H0046 H0052 H0083 H0090 H0169 H0204 H0214 H0264 H0265 H0266 H0352 H0370 H0393 H0421 H0431 H0435 H0448 H0494 H0583 H0620 H0635 H0642 H0653 H0656 H0658 L0021 L0364 L0372 L0374 L0462 L0588 L0596 L0599 L0622 L0644 L0647 L0659 L0663 L0665 L0666 L0731 L0740 L0747 L0750 L0751 L0752 L0753 L0754 L0758 L0759 L0765 L0766 L0769 L0771 L0772 L0773 L0783 L0806 S0038 S0040 S0142 S0280 S0356 S0358 S0366 S0442 S3014 S6028



HBAMB15	H0328 H0410 H0530 L0455 L0740
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**Table 3**

SEQ ID NO: X	Cytologic Band or Chromosome:	OMIM Reference(s):
19	1q21	104770 107670 110700 135940 145001 146790 152445 159001 174000 179755 182860 191315 230800 266200 600897 601105 601412 601652 602491
21	9q33-q34.1	103000 114350 120900 131195 146150 185000 189980 223900 253800 268900 600184 602575
57	16q13	114835 132700 172490 600968
66	12	

**Table 4**

<b>Library Code</b>	<b>Library Description</b>
	BL29 Burkitt's lymphoma, Pascalis Sideras
H0002	Human Adult Heart
H0006	Human Frontal Lobe of Brain
H0009	Human Fetal Brain
H0012	Human Fetal Kidney
H0013	Human 8 Week Whole Embryo
H0014	Human Gall Bladder
H0015	Human Gall Bladder, fraction II
H0023	Human Fetal Lung
H0024	Human Fetal Lung III
H0028	Human Old Ovary
H0030	Human Placenta
H0031	Human Placenta
H0032	Human Prostate
H0036	Human Adult Small Intestine
H0038	Human Testes
H0039	Human Pancreas Tumor
H0040	Human Testes Tumor
H0041	Human Fetal Bone
H0042	Human Adult Pulmonary
H0044	Human Cornea
H0046	Human Endometrial Tumor
H0050	Human Fetal Heart
H0051	Human Hippocampus
H0052	Human Cerebellum
H0056	Human Umbilical Vein, Endo. remake
H0057	Human Fetal Spleen
H0059	Human Uterine Cancer
H0061	Human Macrophage
H0063	Human Thymus
H0068	Human Skin Tumor
H0069	Human Activated T-Cells
H0070	Human Pancreas
H0081	Human Fetal Epithelium (Skin)
H0083	HUMAN JURKAT MEMBRANE BOUND POLYSOMES
H0085	Human Colon
H0086	Human epithelioid sarcoma
H0087	Human Thymus
H0090	Human T-Cell Lymphoma
H0096	Human Parotid Cancer
H0098	Human Adult Liver, subtracted
H0100	Human Whole Six Week Old Embryo
H0103	Human Fetal Brain, subtracted
H0105	Human Fetal Heart, subtracted
H0111	Human Placenta, subtracted
H0116	Human Thymus Tumor, subtracted
H0122	Human Adult Skeletal Muscle

H0123	Human Fetal Dura Mater
H0124	Human Rhabdomyosarcoma
H0130	LNCAP untreated
H0131	LNCAP + 0.3nM R1881
H0134	Raji Cells, cyclohexamide treated
H0135	Human Synovial Sarcoma
H0139	Activated T-Cells, 4 hrs.
H0144	Nine Week Old Early Stage Human
H0149	7 Week Old Early Stage Human, subtracted
H0150	Human Epididymus
H0156	Human Adrenal Gland Tumor
H0163	Human Synovium
H0165	Human Prostate Cancer, Stage B2
H0166	Human Prostate Cancer, Stage B2 fraction
H0169	Human Prostate Cancer, Stage C fraction
H0170	12 Week Old Early Stage Human
H0171	12 Week Old Early Stage Human, II
H0178	Human Fetal Brain
H0179	Human Neutrophil
H0181	Human Primary Breast Cancer
H0188	Human Normal Breast
H0194	Human Cerebellum, subtracted
H0196	Human Cardiomyopathy, subtracted
H0200	Human Greater Omentum, fract II remake,
H0201	Human Hippocampus, subtracted
H0204	Human Colon Cancer, subtracted
H0208	Early Stage Human Lung, subtracted
H0212	Human Prostate, subtracted
H0213	Human Pituitary, subtracted
H0214	Raji cells, cyclohexamide treated, subtracted
H0220	Activated T-Cells, 4 hrs, subtracted
H0224	Activated T-Cells, 12 hrs, subtracted
H0231	Human Colon, subtraction
H0242	Human Fetal Heart, Differential (Fetal-Specific)
H0250	Human Activated Monocytes
H0251	Human Chondrosarcoma
H0252	Human Osteosarcoma
H0253	Human adult testis, large inserts
H0254	breast lymph node CDNA library
H0255	breast lymph node CDNA library
H0261	H. cerebellum, Enzyme subtracted
H0263	human colon cancer
H0264	human tonsils
H0265	Activated T-Cell (12hs)/Thiouridine labelledEco
H0266	Human Microvascular Endothelial Cells, fract. A
H0267	Human Microvascular Endothelial Cells, fract. B
H0268	Human Umbilical Vein Endothelial Cells, fract. A
H0269	Human Umbilical Vein Endothelial Cells, fract. B
H0271	Human Neutrophil, Activated
H0274	Human Adult Spleen, fractionII
H0280	K562 + PMA (36 hrs)
H0284	Human OB MG63 control fraction I

H0286	Human OB MG63 treated (10 nM E2) fraction I
H0288	Human OB HOS control fraction I
H0290	Human OB HOS treated (1 nM E2) fraction I
H0292	Human OB HOS treated (10 nM E2) fraction I
H0294	Amniotic Cells - TNF induced
H0295	Amniotic Cells - Primary Culture
H0305	CD34 positive cells (Cord Blood)
H0306	CD34 depleted Buffy Coat (Cord Blood)
H0309	Human Chronic Synovitis
H0310	human caudate nucleus
H0316	HUMAN STOMACH
H0318	HUMAN B CELL LYMPHOMA
H0320	Human frontal cortex
H0321	HUMAN SCHWANOMA
H0327	human corpus colosum
H0328	human ovarian cancer
H0329	Dermatofibrosarcoma Protuberance
H0331	Hepatocellular Tumor
H0333	Hemangiopericytoma
H0341	Bone Marrow Cell Line (RS4,11)
H0343	stomach cancer (human)
H0351	Glioblastoma
H0352	wilm's tumor
H0355	Human Liver
H0356	Human Kidney
H0357	H. Normalized Fetal Liver, II
H0359	KMH2 cell line
H0361	Human rejected kidney
H0362	HeLa cell line
H0366	L428 cell line
H0370	H. Lymph node breast Cancer
H0373	Human Heart
H0374	Human Brain
H0375	Human Lung
H0381	Bone Cancer
H0388	Human Rejected Kidney, 704 re-excision
H0389	H. Brain, X-Chromosome hybridization
H0391	H. Meningioma, M6
H0392	H. Meningioma, M1
H0393	Fetal Liver, subtraction II
H0396	L1 Cell line
H0400	Human Striatum Depression, re-rescue
H0402	CD34 depleted Buffy Coat (Cord Blood), re-excision
H0403	H. Umbilical Vein Endothelial Cells, IL4 induced
H0410	H. Male bladder, adult
H0411	H Female Bladder, Adult
H0412	Human umbilical vein endothelial cells, IL-4 induced
H0413	Human Umbilical Vein Endothelial Cells, uninduced
H0415	H. Ovarian Tumor, II, OV5232
H0416	Human Neutrophils, Activated, re-excision
H0421	Human Bone Marrow, re-excision
H0422	T-Cell PHA 16 hrs

H0423	T-Cell PHA 24 hrs
H0424	Human Pituitary, subt IX
H0427	Human Adipose
H0428	Human Ovary
H0429	K562 + PMA (36 hrs),re-excision
H0431	H. Kidney Medulla, re-excision
H0435	Ovarian Tumor 10-3-95
H0436	Resting T-Cell Library,II
H0437	H Umbilical Vein Endothelial Cells, frac A, re-excision
H0438	H. Whole Brain #2, re-excision
H0441	H. Kidney Cortex, subtracted
H0444	Spleen metastatic melanoma
H0445	Spleen, Chronic lymphocytic leukemia
H0448	Salivary gland, subtracted
H0449	CD34+ cell, I
H0453	H. Kidney Pyramid, subtracted
H0457	Human Eosinophils
H0458	CD34+ cell, I, frac II
H0478	Salivary Gland, Lib 2
H0479	Salivary Gland, Lib 3
H0483	Breast Cancer cell line, MDA 36
H0484	Breast Cancer Cell line, angiogenic
H0485	Hodgkin's Lymphoma I
H0486	Hodgkin's Lymphoma II
H0488	Human Tonsils, Lib 2
H0489	Crohn's Disease
H0494	Keratinocyte
H0497	HEL cell line
H0506	Ulcerative Colitis
H0509	Liver, Hepatoma
H0510	Human Liver, normal
H0517	Nasal polyps
H0518	pBMC stimulated w/ poly I/C
H0519	NTERA2, control
H0520	NTERA2 + retinoic acid, 14 days
H0521	Primary Dendritic Cells, lib 1
H0522	Primary Dendritic cells,frac 2
H0529	Myeloid Progenitor Cell Line
H0530	Human Dermal Endothelial Cells,untreated
H0538	Merkel Cells
H0539	Pancreas Islet Cell Tumor
H0542	T Cell helper I
H0543	T cell helper II
H0544	Human endometrial stromal cells
H0545	Human endometrial stromal cells-treated with progesterone
H0546	Human endometrial stromal cells-treated with estradiol
H0547	NTERA2 teratocarcinoma cell line+retinoic acid (14 days)
H0549	H. Epididymus, caput & corpus
H0550	H. Epididymus, cauda
H0551	Human Thymus Stromal Cells
H0553	Human Placenta
H0555	Rejected Kidney, lib 4

H0556	Activated T-cell(12h)/Thiouridine-re-excision
H0560	KMH2
H0561	L428
H0569	Human Fetal Brain, normalized CO
H0571	Human Fetal Brain, normalized C500HE
H0574	Hepatocellular Tumor, re-excision
H0575	Human Adult Pulmonary, re-excision
H0576	Resting T-Cell, re-excision
H0580	Dendritic cells, pooled
H0581	Human Bone Marrow, treated
H0583	B Cell lymphoma
H0586	Healing groin wound, 6.5 hours post incision
H0587	Healing groin wound, 7.5 hours post incision
H0589	CD34 positive cells (cord blood), re-ex
H0590	Human adult small intestine, re-excision
H0591	Human T-cell lymphoma, re-excision
H0592	Healing groin wound - zero hr post-incision (control)
H0593	Olfactory epithelium, nasal cavity
H0594	Human Lung Cancer, re-excision
H0596	Human Colon Cancer, re-excision
H0597	Human Colon, re-excision
H0598	Human Stomach, re-excision
H0599	Human Adult Heart, re-excision
H0600	Healing Abdomen wound, 70&90 min post incision
H0601	Healing Abdomen Wound, 15 days post incision
H0602	Healing Abdomen Wound, 21&29 days post incision
H0606	Human Primary Breast Cancer, re-excision
H0615	Human Ovarian Cancer Reexcision
H0616	Human Testes, Reexcision
H0617	Human Primary Breast Cancer Reexcision
H0618	Human Adult Testes, Large Inserts, Reexcision
H0619	Fetal Heart
H0620	Human Fetal Kidney, Reexcision
H0622	Human Pancreas Tumor, Reexcision
H0623	Human Umbilical Vein, Reexcision
H0624	12 Week Early Stage Human II, Reexcision
H0625	Ku 812F Basophils Line
H0626	Saos2 Cells, Untreated
H0627	Saos2 Cells, Vitamin D3 Treated
H0628	Human Pre-Differentiated Adipocytes
H0631	Saos2, Dexamethosone Treated
H0632	Hepatocellular Tumor, re-excision
H0633	Lung Carcinoma A549 TNFalpha activated
H0634	Human Testes Tumor, re-excision
H0635	Human Activated T-Cells, re-excision
H0637	Dendritic Cells From CD34 Cells
H0638	CD40 activated monocyte dendritic cells
H0640	Ficoll Human Stromal Cells, Untreated
H0641	LPS activated derived dendritic cells
H0642	Hep G2 Cells, lambda library
H0644	Human Placenta (re-excision)
H0645	Fetal Heart, re-excision

H0646	Lung, Cancer (4005313 A3): Invasive Poorly Differentiated Lung Adenocarcinoma,
H0647	Lung, Cancer (4005163 B7): Invasive, Poorly Diff. Adenocarcinoma, Metastatic
H0648	Ovary, Cancer: (4004562 B6) Papillary Serous Cystic Neoplasm, Low Malignant Pot
H0650	B-Cells
H0652	Lung, Normal: (4005313 B1)
H0653	Stromal Cells
H0656	B-cells (unstimulated)
H0657	B-cells (stimulated)
H0658	Ovary, Cancer (9809C332): Poorly differentiated adenocarcinoma
H0659	Ovary, Cancer (15395A1F): Grade II Papillary Carcinoma
H0660	Ovary, Cancer: (15799A1F) Poorly differentiated carcinoma
H0661	Breast, Cancer: (4004943 A5)
H0662	Breast, Normal: (4005522B2)
H0663	Breast, Cancer: (4005522 A2)
H0664	Breast, Cancer: (9806C012R)
H0665	Stromal cells 3.88
H0666	Ovary, Cancer: (4004332 A2)
H0667	Stromal cells(HBM3.18)
H0668	stromal cell clone 2.5
H0670	Ovary, Cancer(4004650 A3): Well-Differentiated Micropapillary Serous Carcinoma
H0672	Ovary, Cancer: (4004576 A8)
H0673	Human Prostate Cancer, Stage B2, re-excision
H0674	Human Prostate Cancer, Stage C, re-excision
H0676	Colon, Cancer: (9808C064R)-total RNA
H0677	TNFR degenerate oligo
H0679	screened clones from Tonsil library
H0682	Ovarian cancer, Serous Papillary Adenocarcinoma
H0683	Ovarian cancer, Serous Papillary Adenocarcinoma
H0684	Ovarian cancer, Serous Papillary Adenocarcinoma
H0685	Adenocarcinoma of Ovary, Human Cell Line, # OVCAR-3
H0686	Adenocarcinoma of Ovary, Human Cell Line
H0687	Human normal ovary(#9610G215)
H0688	Human Ovarian Cancer(#9807G017)
H0689	Ovarian Cancer
H0690	Ovarian Cancer, # 9702G001
H0691	Normal Ovary, #9710G208
H0694	Prostate cancer (adenocarcinoma)
H0695	mononucleocytes from patient
H0696	Prostate Adenocarcinoma
H0702	NK15(IL2 treated for 48 hours)
H0707	Stomach Cancer(S007635)
L0005	Clontech human aorta polyA+ mRNA (#6572)
L0017	Human (J. Swensen)
L0021	Human adult (K.Okubo)
L0040	Human colon mucosa
L0041	Human epidermal keratinocyte
L0053	Human pancreatic tumor
L0055	Human promyelocyte
L0103	DKFZphamy1



L0105	Human aorta polyA+ (TFujiwara)
L0142	Human placenta cDNA (TFujiwara)
L0143	Human placenta polyA+ (TFujiwara)
L0157	Human fetal brain (TFujiwara)
L0163	Human heart cDNA (YNakamura)
L0352	Normalized infant brain, Bento Soares
L0361	Stratagene ovary (#937217)
L0362	Stratagene ovarian cancer (#937219)
L0363	NCI CGAP GC2
L0364	NCI CGAP GC5
L0366	Stratagene schizo brain S11
L0367	NCI CGAP Sch1
L0369	NCI CGAP AA1
L0372	NCI CGAP Co12
L0373	NCI CGAP Co11
L0374	NCI CGAP Co2
L0375	NCI CGAP Kid6
L0378	NCI CGAP Lu1
L0381	NCI CGAP HN4
L0382	NCI CGAP Pr25
L0383	NCI CGAP Pr24
L0384	NCI CGAP Pr23
L0387	NCI CGAP GCB0
L0388	NCI CGAP HN6
L0411	1-NIB
L0426	b4HB3MA-Cot51.5-HAP-Ft
L0438	normalized infant brain cDNA
L0439	Soares infant brain 1NIB
L0447	NHB3MK
L0448	3HFLSK20
L0451	N3HFLSK20
L0455	Human retina cDNA randomly primed sublibrary
L0460	Adult heart, Lambda gt11
L0462	WATM1
L0465	TEST1, Human adult Testis tissue
L0471	Human fetal heart, Lambda ZAP Express
L0481	CD34+DIRECTIONAL
L0483	Human pancreatic islet
L0485	STRATAGENE Human skeletal muscle cDNA library, cat. #936215.
L0493	NCI CGAP Ov26
L0498	NCI CGAP HSC3
L0511	NCI CGAP Ov34
L0512	NCI CGAP Ov36
L0515	NCI CGAP Ov32
L0517	NCI CGAP Pr1
L0518	NCI CGAP Pr2
L0519	NCI CGAP Pr3
L0520	NCI CGAP Alv1
L0521	NCI CGAP Ew1
L0523	NCI CGAP Lip2
L0525	NCI CGAP Li2
L0526	NCI CGAP Pr12

L0527	NCI CGAP Ov2
L0529	NCI CGAP Pr6
L0530	NCI CGAP Pr8
L0532	NCI CGAP Thy1
L0534	Chromosome 7 Fetal Brain cDNA Library
L0536	NCI CGAP Br4
L0539	Chromosome 7 Placental cDNA Library
L0540	NCI CGAP Pr10
L0542	NCI CGAP Pr11
L0545	NCI CGAP Pr4.1
L0549	NCI CGAP HN10
L0553	NCI CGAP Co22
L0554	NCI CGAP Li8
L0560	NCI CGAP HN12
L0562	Chromosome 7 HeLa cDNA Library
L0563	Human Bone Marrow Stromal Fibroblast
L0564	Jia bone marrow stroma
L0565	Normal Human Trabecular Bone Cells
L0581	Stratagene liver (#937224)
L0586	HTCDL1
L0588	Stratagene endothelial cell 937223
L0589	Stratagene fetal retina 937202
L0591	Stratagene HeLa cell s3 937216
L0592	Stratagene hNT neuron (#937233)
L0593	Stratagene neuroepithelium (#937231)
L0595	Stratagene NT2 neuronal precursor 937230
L0596	Stratagene colon (#937204)
L0597	Stratagene corneal stroma (#937222)
L0598	Morton Fetal Cochlea
L0599	Stratagene lung (#937210)
L0600	Weizmann Olfactory Epithelium
L0601	Stratagene pancreas (#937208)
L0602	Pancreatic Islet
L0603	Stratagene placenta (#937225)
L0604	Stratagene muscle 937209
L0605	Stratagene fetal spleen (#937205)
L0606	NCI CGAP Lym5
L0607	NCI CGAP Lym6
L0608	Stratagene lung carcinoma 937218
L0612	Schiller oligodendroglioma
L0615	22 week old human fetal liver cDNA library
L0622	HM1
L0623	HM3
L0626	NCI CGAP GC1
L0629	NCI CGAP Mel3
L0635	NCI CGAP PNS1
L0636	NCI CGAP Pit1
L0637	NCI CGAP Brn53
L0638	NCI CGAP Brn35
L0639	NCI CGAP Brn52
L0640	NCI CGAP Br18
L0641	NCI CGAP Co17

L0642	NCI CGAP Co18
L0644	NCI CGAP Co20
L0645	NCI CGAP Co21
L0646	NCI CGAP Co14
L0647	NCI CGAP Sar4
L0648	NCI CGAP Eso2
L0649	NCI CGAP GU1
L0650	NCI CGAP Kid13
L0651	NCI CGAP Kid8
L0653	NCI CGAP Lu28
L0654	NCI CGAP Lu31
L0655	NCI CGAP Lym12
L0656	NCI CGAP Ov38
L0657	NCI CGAP Ov23
L0658	NCI CGAP Ov35
L0659	NCI CGAP Pan1
L0661	NCI CGAP Mel15
L0662	NCI CGAP Gas4
L0663	NCI CGAP Ut2
L0664	NCI CGAP Ut3
L0665	NCI CGAP Ut4
L0666	NCI CGAP Ut1
L0667	NCI CGAP CML1
L0682	Stanley Frontal NB pool 2
L0697	Testis 1
L0717	Gessler Wilms tumor
L0731	Soares pregnant uterus NbHPU
L0738	Human colorectal cancer
L0740	Soares melanocyte 2NbHM
L0741	Soares adult brain N2b4HB55Y
L0742	Soares adult brain N2b5HB55Y
L0743	Soares breast 2NbHBst
L0744	Soares breast 3NbHBst
L0745	Soares retina N2b4HR
L0746	Soares retina N2b5HR
L0747	Soares fetal heart NbHH19W
L0748	Soares fetal liver spleen 1NFLS
L0749	Soares fetal liver spleen 1NFLS S1
L0750	Soares fetal lung NbHL19W
L0751	Soares ovary tumor NbHOT
L0752	Soares parathyroid tumor NbHPA
L0753	Soares pineal gland N3HPG
L0754	Soares placenta Nb2HP
L0755	Soares placenta 8to9weeks 2NbHP8to9W
L0756	Soares multiple sclerosis 2NbHMSP
L0757	Soares senescent fibroblasts NbHSF
L0758	Soares testis NHT
L0759	Soares total fetus Nb2HF8 9w
L0761	NCI CGAP CLL1
L0762	NCI CGAP Br1.1
L0763	NCI CGAP Br2
L0764	NCI CGAP Co3

L0765	NCI CGAP Co4
L0766	NCI CGAP GCB1
L0767	NCI CGAP GC3
L0768	NCI CGAP GC4
L0769	NCI CGAP Brn25
L0770	NCI CGAP Brn23
L0771	NCI CGAP Co8
L0772	NCI CGAP Co10
L0773	NCI CGAP Co9
L0774	NCI CGAP Kid3
L0775	NCI CGAP Kid5
L0776	NCI CGAP Lu5
L0777	Soares NhHMPu S1
L0779	Soares NFL T GBC S1
L0780	Soares NSF F8 9W OT PA P S1
L0782	NCI CGAP Pr21
L0783	NCI CGAP Pr22
L0785	Barstead spleen HPLRB2
L0786	Soares NbHFB
L0788	NCI CGAP Sub2
L0789	NCI CGAP Sub3
L0790	NCI CGAP Sub4
L0791	NCI CGAP Sub5
L0792	NCI CGAP Sub6
L0794	NCI CGAP GC6
L0796	NCI CGAP Brn50
L0800	NCI CGAP Co16
L0803	NCI CGAP Kid11
L0804	NCI CGAP Kid12
L0805	NCI CGAP Lu24
L0806	NCI CGAP Lu19
L0807	NCI CGAP Ov18
L0809	NCI CGAP Pr28
S0001	Brain frontal cortex
S0002	Monocyte activated
S0003	Human Osteoclastoma
S0007	Early Stage Human Brain
S0010	Human Amygdala
S0011	STROMAL -OSTEOCLASTOMA
S0013	Prostate
S0014	Kidney Cortex
S0015	Kidney medulla
S0022	Human Osteoclastoma Stromal Cells - unamplified
S0026	Stromal cell TF274
S0027	Smooth muscle, serum treated
S0028	Smooth muscle, control
S0029	brain stem
S0030	Brain pons
S0031	Spinal cord
S0032	Smooth muscle-ILb induced
S0036	Human Substantia Nigra
S0037	Smooth muscle, IL1b induced

S0038	Human Whole Brain #2 - Oligo dT > 1.5Kb
S0040	Adipocytes
S0042	Testes
S0044	Prostate BPH
S0045	Endothelial cells-control
S0046	Endothelial-induced
S0049	Human Brain, Striatum
S0050	Human Frontal Cortex, Schizophrenia
S0051	Human Hypothalamus, Schizophrenia
S0052	neutrophils control
S0053	Neutrophils IL-1 and LPS induced
S0112	Hypothalamus
S0114	Anergic T-cell
S0116	Bone marrow
S0122	Osteoclastoma-normalized A
S0126	Osteoblasts
S0132	Epithelial-TNF $\alpha$ and INF induced
S0134	Apoptotic T-cell
S0136	PERM TF274
S0140	eosinophil-IL5 induced
S0142	Macrophage-oxLDL
S0144	Macrophage (GM-CSF treated)
S0146	prostate-edited
S0150	LNCAP prostate cell line
S0152	PC3 Prostate cell line
S0176	Prostate, normal, subtraction I
S0192	Synovial Fibroblasts (control)
S0194	Synovial hypoxia
S0196	Synovial IL-1/TNF stimulated
S0198	7TM-pbfd
S0206	Smooth Muscle- HASTE normalized
S0208	Mesangial cell, frac 1
S0210	Mesangial cell, frac 2
S0212	Bone Marrow Stromal Cell, untreated
S0214	Human Osteoclastoma, re-excision
S0216	Neutrophils IL-1 and LPS induced
S0218	Apoptotic T-cell, re-excision
S0220	H. hypothalamus, frac A, re-excision
S0222	H. Frontal cortex, epileptic, re-excision
S0228	PSMIX
S0242	Synovial Fibroblasts (II1/TNF), subt
S0250	Human Osteoblasts II
S0252	7TM-PIMIX
S0260	Spinal Cord, re-excision
S0264	PPMIX
S0268	PRMIX
S0270	PTMIX
S0274	PCMIX
S0276	Synovial hypoxia-RSF subtracted
S0278	H Macrophage (GM-CSF treated), re-excision
S0280	Human Adipose Tissue, re-excision
S0282	Brain Frontal Cortex, re-excision

S0294	Larynx tumor
S0300	Frontal lobe,dementia,re-excision
S0312	Human osteoarthritic,fraction II
S0314	Human osteoarthritis,fraction I
S0316	Human Normal Cartilage,Fraction I
S0318	Human Normal Cartilage Fraction II
S0328	Palate carcinoma
S0330	Palate normal
S0332	Pharynx carcinoma
S0334	Human Normal Cartilage Fraction III
S0338	Human Osteoarthritic Cartilage Fraction III
S0342	Adipocytes,re-excision
S0344	Macrophage-oxLDL, re-excision
S0346	Human Amygdala,re-excision
S0348	Cheek Carcinoma
S0350	Pharynx Carcinoma
S0352	Larynx Carcinoma
S0354	Colon Normal II
S0356	Colon Carcinoma
S0358	Colon Normal III
S0360	Colon Tumor II
S0364	Human Quadriceps
S0366	Human Soleus
S0374	Normal colon
S0376	Colon Tumor
S0378	Pancreas normal PCA4 No
S0380	Pancreas Tumor PCA4 Tu
S0384	Tongue carcinoma
S0388	Human Hypothalamus,schizophrenia, re-excision
S0390	Smooth muscle, control, re-excision
S0392	Salivary Gland
S0402	Adrenal Gland,normal
S0412	Temporal cortex-Alzheimr, subtracted
S0414	Hippocampus, Alzheimer Subtracted
S0418	CHME Cell Line,treated 5 hrs
S0420	CHME Cell Line,untreated
S0422	Mo7e Cell Line GM-CSF treated (1ng/ml)
S0424	TF-1 Cell Line GM-CSF Treated
S0426	Monocyte activated, re-excision
S0428	Neutrophils control, re-excision
S0430	Aryepiglottis Normal
S0432	Sinus piniformis Tumour
S0434	Stomach Normal
S0438	Liver Normal Met5No
S0442	Colon Normal
S0446	Tongue Tumour
S0450	Larynx Tumour
S0452	Thymus
S0456	Tongue Normal
S0458	Thyroid Normal (SDCA2 No)
S0462	Thyroid Thyroiditis
S0466	Larynx Tumor

S0468	Ea.hy.926 cell line
S0474	Human blood platelets
S3012	Smooth Muscle Serum Treated, Norm
S3014	Smooth muscle, serum induced,re-exc
S6014	H. hypothalamus, frac A
S6024	Alzheimers, spongy change
S6028	Human Manic Depression Tissue
T0002	Activated T-cells
T0003	Human Fetal Lung
T0004	Human White Fat
T0006	Human Pineal Gland
T0008	Colorectal Tumor
T0010	Human Infant Brain
T0023	Human Pancreatic Carcinoma
T0039	HSA 172 Cells
T0040	HSC172 cells
T0041	Jurkat T-cell G1 phase
T0042	Jurkat T-Cell, S phase
T0048	Human Aortic Endothelium
T0049	Aorta endothelial cells + TNF-a
T0060	Human White Adipose
T0067	Human Thyroid
T0069	Human Uterus, normal
T0082	Human Adult Retina
T0091	Liver, hepatocellular carcinoma
T0109	Human (HCC) cell line liver (mouse) metastasis, remake
T0110	Human colon carcinoma (HCC) cell line, remake
T0114	Human (Caco-2) cell line, adenocarcinoma, colon, remake

**Table 5**

OMIM ID	OMIM Description
103000	Hemolytic anemia due to adenylate kinase deficiency (3)
104770	?Amyloidosis, secondary, susceptibility to (1)
107670	Apolipoprotein A-II deficiency (3)
110700	Vivax malaria, susceptibility to (1)
114350	Leukemia, acute myeloid (2)
114835	Monocyte carboxyesterase deficiency (1) (?)
120900	C5 deficiency (1)
131195	Hereditary hemorrhagic telangiectasia-1, 187300 (3)
132700	Cylindromatosis (2)
135940	Ichthyosis vulgaris, 146700 (1) (?)
145001	Hyperparathyroidism-jaw tumor syndrome (2)
146150	Hypomelanosis of Ito (2) (?)
146790	Lupus nephritis, susceptibility to (3)
152445	Erythrokeratoderma, progressive symmetric, 602036 (3) Vohwinkel syndrome, 124500 (3)
159001	Muscular dystrophy, limb-girdle, type 1B (2)
172490	Phosphorylase kinase deficiency of liver and muscle, 261750 (2) (?)
174000	Medullary cystic kidney disease, AD (2)
179755	Renal cell carcinoma, papillary, 1 (2)
182860	Elliptocytosis-2 (3) Pyropoikilocytosis (3) Spherocytosis, recessive (3)
185000	Stomatocytosis I (1) (?)
189980	Leukemia, chronic myeloid (3)
191315	Insensitivity to pain, congenital, with anhidrosis, 256800 (3)
223900	Dysautonomia, familial (2)
230800	Gaucher disease (3) Gaucher disease with cardiovascular calcification (3)
253800	Fukuyama type congenital muscular dystrophy (2) Walker-Warburg syndrome, 236670 (2) (?)
266200	Anemia, hemolytic, due to PK deficiency (3)
268900	[Sarcosinemia] (2)
600184	Carnitine acetyltransferase deficiency (1) (?)
600897	Cataract, zonular pulverulent-1, 116200 (3)
600968	Gitelman syndrome, 263800 (3)
601105	Pycnodysostosis, 265800 (3)
601412	Deafness, autosomal dominant 7 (2)
601652	Glaucoma 1A, primary open angle, juvenile-onset, 137750 (3)
602491	Hyperlipidemia, familial combined, 1 (2)
602575	Nail-patella syndrome with open-angle glaucoma, 137750 (3) Nail-patella syndrome, 161200 (3)



**[0701]** The polypeptides of the invention can be prepared in any suitable manner. Such polypeptides include isolated naturally occurring polypeptides, recombinantly produced polypeptides, synthetically produced polypeptides, or polypeptides produced by a combination of these methods. Means for preparing such polypeptides are well understood in the art.

**[0702]** The polypeptides may be in the form of the secreted protein, including the mature form, or may be a part of a larger protein, such as a fusion protein (see below). It is often advantageous to include an additional amino acid sequence which contains secretory or leader sequences, pro-sequences, sequences which aid in purification, such as multiple histidine residues, or an additional sequence for stability during recombinant production.

**[0703]** The polypeptides of the present invention are preferably provided in an isolated form, and preferably are substantially purified. A recombinantly produced version of a polypeptide, including the secreted polypeptide, can be substantially purified using techniques described herein or otherwise known in the art, such as, for example, by the one-step method described in Smith and Johnson, Gene 67:31-40 (1988). Polypeptides of the invention also can be purified from natural, synthetic or recombinant sources using techniques described herein or otherwise known in the art, such as, for example, antibodies of the invention raised against the secreted protein.

**[0704]** The present invention provides a polynucleotide comprising, or alternatively consisting of, the nucleic acid sequence of SEQ ID NO:X, and/or a cDNA contained in ATCC deposit Z. The present invention also provides a polypeptide comprising, or alternatively, consisting of, the polypeptide sequence of SEQ ID NO:Y and/or a polypeptide encoded by the cDNA contained in ATCC deposit Z. Polynucleotides encoding a polypeptide comprising, or alternatively consisting of the polypeptide sequence of SEQ ID NO:Y and/or a polypeptide sequence encoded by the cDNA contained in ATCC deposit Z are also encompassed by the invention.

**[0705] Signal Sequences**

**[0706]** The present invention also encompasses mature forms of the polypeptide having the polypeptide sequence of SEQ ID NO:Y and/or the polypeptide sequence encoded by the cDNA in a deposited clone. Polynucleotides encoding the mature

forms (such as, for example, the polynucleotide sequence in SEQ ID NO:X and/or the polynucleotide sequence contained in the cDNA of a deposited clone) are also encompassed by the invention. According to the signal hypothesis, proteins secreted by mammalian cells have a signal or secretory leader sequence which is cleaved from the mature protein once export of the growing protein chain across the rough endoplasmic reticulum has been initiated. Most mammalian cells and even insect cells cleave secreted proteins with the same specificity. However, in some cases, cleavage of a secreted protein is not entirely uniform, which results in two or more mature species of the protein. Further, it has long been known that cleavage specificity of a secreted protein is ultimately determined by the primary structure of the complete protein, that is, it is inherent in the amino acid sequence of the polypeptide.

[0707] Methods for predicting whether a protein has a signal sequence, as well as the cleavage point for that sequence, are available. For instance, the method of McGeoch, *Virus Res.* 3:271-286 (1985), uses the information from a short N-terminal charged region and a subsequent uncharged region of the complete (uncleaved) protein. The method of von Heinje, *Nucleic Acids Res.* 14:4683-4690 (1986) uses the information from the residues surrounding the cleavage site, typically residues -13 to +2, where +1 indicates the amino terminus of the secreted protein. The accuracy of predicting the cleavage points of known mammalian secretory proteins for each of these methods is in the range of 75-80%. (von Heinje, *supra.*) However, the two methods do not always produce the same predicted cleavage point(s) for a given protein.

[0708] In the present case, the deduced amino acid sequence of the secreted polypeptide was analyzed by a computer program called SignalP (Henrik Nielsen et al., *Protein Engineering* 10:1-6 (1997)), which predicts the cellular location of a protein based on the amino acid sequence. As part of this computational prediction of localization, the methods of McGeoch and von Heinje are incorporated. The analysis of the amino acid sequences of the secreted proteins described herein by this program provided the results shown in Table 1.

[0709] As one of ordinary skill would appreciate, however, cleavage sites sometimes vary from organism to organism and cannot be predicted with absolute certainty.

Accordingly, the present invention provides secreted polypeptides having a sequence shown in SEQ ID NO:Y which have an N-terminus beginning within 5 residues (i.e., + or - 5 residues) of the predicted cleavage point. Similarly, it is also recognized that in some cases, cleavage of the signal sequence from a secreted protein is not entirely uniform, resulting in more than one secreted species. These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

[0710] Moreover, the signal sequence identified by the above analysis may not necessarily predict the naturally occurring signal sequence. For example, the naturally occurring signal sequence may be further upstream from the predicted signal sequence. However, it is likely that the predicted signal sequence will be capable of directing the secreted protein to the ER. Nonetheless, the present invention provides the mature protein produced by expression of the polynucleotide sequence of SEQ ID NO:X and/or the polynucleotide sequence contained in the cDNA of a deposited clone, in a mammalian cell (e.g., COS cells, as described below). These polypeptides, and the polynucleotides encoding such polypeptides, are contemplated by the present invention.

**[0711] Polynucleotide and Polypeptide Variants**

[0712] The present invention is directed to variants of the polynucleotide sequence disclosed in SEQ ID NO:X, the complementary strand thereto, and/or the cDNA sequence contained in a deposited clone.

[0713] The present invention also encompasses variants of the polypeptide sequence disclosed in SEQ ID NO:Y and/or encoded by a deposited clone.

[0714] "Variant" refers to a polynucleotide or polypeptide differing from the polynucleotide or polypeptide of the present invention, but retaining essential properties thereof. Generally, variants are overall closely similar, and, in many regions, identical to the polynucleotide or polypeptide of the present invention.

**[0715]** The present invention is also directed to nucleic acid molecules which comprise, or alternatively consist of, a nucleotide sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for example, the nucleotide coding sequence in SEQ ID NO:X or the complementary strand thereto, the nucleotide coding sequence contained in a deposited cDNA clone or the complementary strand thereto, a nucleotide sequence encoding the polypeptide of SEQ ID NO:Y, a nucleotide sequence encoding the polypeptide encoded by the cDNA contained in a deposited clone, and/or polynucleotide fragments of any of these nucleic acid molecules (e.g., those fragments described herein).

Polynucleotides which hybridize to these nucleic acid molecules under stringent hybridization conditions or lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

**[0716]** The present invention is also directed to polypeptides which comprise, or alternatively consist of, an amino acid sequence which is at least 80%, 85%, 90%, 95%, 96%, 97%, 98%, 99% identical to, for example, the polypeptide sequence shown in SEQ ID NO:Y, the polypeptide sequence encoded by the cDNA contained in a deposited clone, and/or polypeptide fragments of any of these polypeptides (e.g., those fragments described herein).

**[0717]** By a nucleic acid having a nucleotide sequence at least, for example, 95% "identical" to a reference nucleotide sequence of the present invention, it is intended that the nucleotide sequence of the nucleic acid is identical to the reference sequence except that the nucleotide sequence may include up to five point mutations per each 100 nucleotides of the reference nucleotide sequence encoding the polypeptide. In other words, to obtain a nucleic acid having a nucleotide sequence at least 95% identical to a reference nucleotide sequence, up to 5% of the nucleotides in the reference sequence may be deleted or substituted with another nucleotide, or a number of nucleotides up to 5% of the total nucleotides in the reference sequence may be inserted into the reference sequence. The query sequence may be an entire sequence shown in Table 1, the ORF (open reading frame), or any fragment specified as described herein.

**[0718]** As a practical matter, whether any particular nucleic acid molecule or polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to a nucleotide sequence of the present invention can be determined conventionally using known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245(1990)). In a sequence alignment the query and subject sequences are both DNA sequences. An RNA sequence can be compared by converting U's to T's. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB alignment of DNA sequences to calculate percent identity are: Matrix=Unitary, k-tuple=4, Mismatch Penalty=1, Joining Penalty=30, Randomization Group Length=0, Cutoff Score=1, Gap Penalty=5, Gap Size Penalty 0.05, Window Size=500 or the length of the subject nucleotide sequence, whichever is shorter.

**[0719]** If the subject sequence is shorter than the query sequence because of 5' or 3' deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for 5' and 3' truncations of the subject sequence when calculating percent identity. For subject sequences truncated at the 5' or 3' ends, relative to the query sequence, the percent identity is corrected by calculating the number of bases of the query sequence that are 5' and 3' of the subject sequence, which are not matched/aligned, as a percent of the total bases of the query sequence. Whether a nucleotide is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This corrected score is what is used for the purposes of the present invention. Only bases outside the 5' and 3' bases of the subject sequence, as displayed by the FASTDB alignment, which are not matched/aligned with the query sequence, are calculated for the purposes of manually adjusting the percent identity score.

**[0720]** For example, a 90 base subject sequence is aligned to a 100 base query sequence to determine percent identity. The deletions occur at the 5' end of the subject sequence and therefore, the FASTDB alignment does not show a matched/alignment of the first 10 bases at 5' end. The 10 unpaired bases represent 10% of the sequence (number of bases at the 5' and 3' ends not matched/total number of bases in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 bases were perfectly matched the final percent identity would be 90%. In another example, a 90 base subject sequence is compared with a 100 base query sequence. This time the deletions are internal deletions so that there are no bases on the 5' or 3' of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only bases 5' and 3' of the subject sequence which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

**[0721]** By a polypeptide having an amino acid sequence at least, for example, 95% "identical" to a query amino acid sequence of the present invention, it is intended that the amino acid sequence of the subject polypeptide is identical to the query sequence except that the subject polypeptide sequence may include up to five amino acid alterations per each 100 amino acids of the query amino acid sequence. In other words, to obtain a polypeptide having an amino acid sequence at least 95% identical to a query amino acid sequence, up to 5% of the amino acid residues in the subject sequence may be inserted, deleted, (indels) or substituted with another amino acid. These alterations of the reference sequence may occur at the amino or carboxy terminal positions of the reference amino acid sequence or anywhere between those terminal positions, interspersed either individually among residues in the reference sequence or in one or more contiguous groups within the reference sequence.

**[0722]** As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical to, for instance, an amino acid sequences shown in Table 1 (SEQ ID NO:Y) or to the amino acid sequence encoded by cDNA contained in a deposited clone can be determined conventionally using

known computer programs. A preferred method for determining the best overall match between a query sequence (a sequence of the present invention) and a subject sequence, also referred to as a global sequence alignment, can be determined using the FASTDB computer program based on the algorithm of Brutlag et al. (Comp. App. Biosci. 6:237-245(1990)). In a sequence alignment the query and subject sequences are either both nucleotide sequences or both amino acid sequences. The result of said global sequence alignment is in percent identity. Preferred parameters used in a FASTDB amino acid alignment are: Matrix=PAM 0, k-tuple=2, Mismatch Penalty=1, Joining Penalty=20, Randomization Group Length=0, Cutoff Score=1, Window Size=sequence length, Gap Penalty=5, Gap Size Penalty=0.05, Window Size=500 or the length of the subject amino acid sequence, whichever is shorter.

**[0723]** If the subject sequence is shorter than the query sequence due to N- or C-terminal deletions, not because of internal deletions, a manual correction must be made to the results. This is because the FASTDB program does not account for N- and C-terminal truncations of the subject sequence when calculating global percent identity. For subject sequences truncated at the N- and C-termini, relative to the query sequence, the percent identity is corrected by calculating the number of residues of the query sequence that are N- and C-terminal of the subject sequence, which are not matched/aligned with a corresponding subject residue, as a percent of the total bases of the query sequence. Whether a residue is matched/aligned is determined by results of the FASTDB sequence alignment. This percentage is then subtracted from the percent identity, calculated by the above FASTDB program using the specified parameters, to arrive at a final percent identity score. This final percent identity score is what is used for the purposes of the present invention. Only residues to the N- and C-termini of the subject sequence, which are not matched/aligned with the query sequence, are considered for the purposes of manually adjusting the percent identity score. That is, only query residue positions outside the farthest N- and C-terminal residues of the subject sequence.

**[0724]** For example, a 90 amino acid residue subject sequence is aligned with a 100 residue query sequence to determine percent identity. The deletion occurs at the N-terminus of the subject sequence and therefore, the FASTDB alignment does not

show a matching/alignment of the first 10 residues at the N-terminus. The 10 unpaired residues represent 10% of the sequence (number of residues at the N- and C-termini not matched/total number of residues in the query sequence) so 10% is subtracted from the percent identity score calculated by the FASTDB program. If the remaining 90 residues were perfectly matched the final percent identity would be 90%. In another example, a 90 residue subject sequence is compared with a 100 residue query sequence. This time the deletions are internal deletions so there are no residues at the N- or C-termini of the subject sequence which are not matched/aligned with the query. In this case the percent identity calculated by FASTDB is not manually corrected. Once again, only residue positions outside the N- and C-terminal ends of the subject sequence, as displayed in the FASTDB alignment, which are not matched/aligned with the query sequence are manually corrected for. No other manual corrections are to be made for the purposes of the present invention.

**[0725]** The variants may contain alterations in the coding regions, non-coding regions, or both. Especially preferred are polynucleotide variants containing alterations which produce silent substitutions, additions, or deletions, but do not alter the properties or activities of the encoded polypeptide. Nucleotide variants produced by silent substitutions due to the degeneracy of the genetic code are preferred. Moreover, variants in which 5-10, 1-5, or 1-2 amino acids are substituted, deleted, or added in any combination are also preferred. Polynucleotide variants can be produced for a variety of reasons, e.g., to optimize codon expression for a particular host (change codons in the human mRNA to those preferred by a bacterial host such as *E. coli*).

**[0726]** Naturally occurring variants are called "allelic variants," and refer to one of several alternate forms of a gene occupying a given locus on a chromosome of an organism. (Genes II, Lewin, B., ed., John Wiley & Sons, New York (1985).) These allelic variants can vary at either the polynucleotide and/or polypeptide level and are included in the present invention. Alternatively, non-naturally occurring variants may be produced by mutagenesis techniques or by direct synthesis.

**[0727]** Using known methods of protein engineering and recombinant DNA technology, variants may be generated to improve or alter the characteristics of the



polypeptides of the present invention. For instance, one or more amino acids can be deleted from the N-terminus or C-terminus of the secreted protein without substantial loss of biological function. The authors of Ron et al., J. Biol. Chem. 268: 2984-2988 (1993), reported variant KGF proteins having heparin binding activity even after deleting 3, 8, or 27 amino-terminal amino acid residues. Similarly, Interferon gamma exhibited up to ten times higher activity after deleting 8-10 amino acid residues from the carboxy terminus of this protein. (Dobeli et al., J. Biotechnology 7:199-216 (1988).)

[0728] Moreover, ample evidence demonstrates that variants often retain a biological activity similar to that of the naturally occurring protein. For example, Gayle and coworkers (J. Biol. Chem 268:22105-22111 (1993)) conducted extensive mutational analysis of human cytokine IL-1a. They used random mutagenesis to generate over 3,500 individual IL-1a mutants that averaged 2.5 amino acid changes per variant over the entire length of the molecule. Multiple mutations were examined at every possible amino acid position. The investigators found that "[m]ost of the molecule could be altered with little effect on either [binding or biological activity]." (See, Abstract.) In fact, only 23 unique amino acid sequences, out of more than 3,500 nucleotide sequences examined, produced a protein that significantly differed in activity from wild-type.

[0729] Furthermore, even if deleting one or more amino acids from the N-terminus or C-terminus of a polypeptide results in modification or loss of one or more biological functions, other biological activities may still be retained. For example, the ability of a deletion variant to induce and/or to bind antibodies which recognize the secreted form will likely be retained when less than the majority of the residues of the secreted form are removed from the N-terminus or C-terminus. Whether a particular polypeptide lacking N- or C-terminal residues of a protein retains such immunogenic activities can readily be determined by routine methods described herein and otherwise known in the art.

[0730] Thus, the invention further includes polypeptide variants which show substantial biological activity. Such variants include deletions, insertions, inversions, repeats, and substitutions selected according to general rules known in the

art so as have little effect on activity. For example, guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie et al., Science 247:1306-1310 (1990), wherein the authors indicate that there are two main strategies for studying the tolerance of an amino acid sequence to change.

**[0731]** The first strategy exploits the tolerance of amino acid substitutions by natural selection during the process of evolution. By comparing amino acid sequences in different species, conserved amino acids can be identified. These conserved amino acids are likely important for protein function. In contrast, the amino acid positions where substitutions have been tolerated by natural selection indicates that these positions are not critical for protein function. Thus, positions tolerating amino acid substitution could be modified while still maintaining biological activity of the protein.

**[0732]** The second strategy uses genetic engineering to introduce amino acid changes at specific positions of a cloned gene to identify regions critical for protein function. For example, site directed mutagenesis or alanine-scanning mutagenesis (introduction of single alanine mutations at every residue in the molecule) can be used. (Cunningham and Wells, Science 244:1081-1085 (1989).) The resulting mutant molecules can then be tested for biological activity.

**[0733]** As the authors state, these two strategies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at certain amino acid positions in the protein. For example, most buried (within the tertiary structure of the protein) amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Moreover, tolerated conservative amino acid substitutions involve replacement of the aliphatic or hydrophobic amino acids Ala, Val, Leu and Ile; replacement of the hydroxyl residues Ser and Thr; replacement of the acidic residues Asp and Glu; replacement of the amide residues Asn and Gln, replacement of the basic residues Lys, Arg, and His; replacement of the aromatic residues Phe, Tyr, and Trp, and replacement of the small-sized amino acids Ala, Ser, Thr, Met, and Gly.

**[0734]** Besides conservative amino acid substitution, variants of the present invention include (i) substitutions with one or more of the non-conserved amino acid residues,

where the substituted amino acid residues may or may not be one encoded by the genetic code, or (ii) substitution with one or more of amino acid residues having a substituent group, or (iii) fusion of the mature polypeptide with another compound, such as a compound to increase the stability and/or solubility of the polypeptide (for example, polyethylene glycol), or (iv) fusion of the polypeptide with additional amino acids, such as, for example, an IgG Fc fusion region peptide, or leader or secretory sequence, or a sequence facilitating purification. Such variant polypeptides are deemed to be within the scope of those skilled in the art from the teachings herein.

[0735] For example, polypeptide variants containing amino acid substitutions of charged amino acids with other charged or neutral amino acids may produce proteins with improved characteristics, such as less aggregation. Aggregation of pharmaceutical formulations both reduces activity and increases clearance due to the aggregate's immunogenic activity. (Pinckard et al., Clin. Exp. Immunol. 2:331-340 (1967); Robbins et al., Diabetes 36: 838-845 (1987); Cleland et al., Crit. Rev. Therapeutic Drug Carrier Systems 10:307-377 (1993).)

[0736] A further embodiment of the invention relates to a polypeptide which comprises the amino acid sequence of the present invention having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions. Of course, in order of ever-increasing preference, it is highly preferable for a peptide or polypeptide to have an amino acid sequence which comprises the amino acid sequence of the present invention, which contains at least one, but not more than 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions. In specific embodiments, the number of additions, substitutions, and/or deletions in the amino acid sequence of the present invention or fragments thereof (e.g., the mature form and/or other fragments described herein), is 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, conservative amino acid substitutions are preferable.

#### **[0737] Polynucleotide and Polypeptide Fragments**

[0738] The present invention is also directed to polynucleotide fragments of the polynucleotides of the invention.

[0739] In the present invention, a "polynucleotide fragment" refers to a short polynucleotide having a nucleic acid sequence which: is a portion of that contained in a deposited clone, or encoding the polypeptide encoded by the cDNA in a deposited clone; is a portion of that shown in SEQ ID NO:X or the complementary strand thereto, or is a portion of a polynucleotide sequence encoding the polypeptide of SEQ ID NO:Y. The nucleotide fragments of the invention are preferably at least about 15 nt, and more preferably at least about 20 nt, still more preferably at least about 30 nt, and even more preferably, at least about 40 nt, at least about 50 nt, at least about 75 nt, or at least about 150 nt in length. A fragment "at least 20 nt in length," for example, is intended to include 20 or more contiguous bases from the cDNA sequence contained in a deposited clone or the nucleotide sequence shown in SEQ ID NO:X. In this context "about" includes the particularly recited value, a value larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. These nucleotide fragments have uses that include, but are not limited to, as diagnostic probes and primers as discussed herein. Of course, larger fragments (e.g., 50, 150, 500, 600, 2000 nucleotides) are preferred.

[0740] Moreover, representative examples of polynucleotide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, a sequence from about nucleotide number 1-50, 51-100, 101-150, 151-200, 201-250, 251-300, 301-350, 351-400, 401-450, 451-500, 501-550, 551-600, 651-700, 701-750, 751-800, 800-850, 851-900, 901-950, 951-1000, 1001-1050, 1051-1100, 1101-1150, 1151-1200, 1201-1250, 1251-1300, 1301-1350, 1351-1400, 1401-1450, 1451-1500, 1501-1550, 1551-1600, 1601-1650, 1651-1700, 1701-1750, 1751-1800, 1801-1850, 1851-1900, 1901-1950, 1951-2000, or 2001 to the end of SEQ ID NO:X, or the complementary strand thereto, or the cDNA contained in a deposited clone. In this context "about" includes the particularly recited ranges, and ranges larger or smaller by several (5, 4, 3, 2, or 1) nucleotides, at either terminus or at both termini. Preferably, these fragments encode a polypeptide which has biological activity. More preferably, these polynucleotides can be used as probes or primers as discussed

herein. Polynucleotides which hybridize to these nucleic acid molecules under stringent hybridization conditions or lower stringency conditions are also encompassed by the invention, as are polypeptides encoded by these polynucleotides.

**[0741]** In the present invention, a "polypeptide fragment" refers to an amino acid sequence which is a portion of that contained in SEQ ID NO:Y or encoded by the cDNA contained in a deposited clone. Protein (polypeptide) fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments comprising, or alternatively consisting of, from about amino acid number 1-20, 21-40, 41-60, 61-80, 81-100, 102-120, 121-140, 141-160, or 161 to the end of the coding region. Moreover, polypeptide fragments can be about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges or values, and ranges or values larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes. Polynucleotides encoding these polypeptides are also encompassed by the invention.

**[0742]** Preferred polypeptide fragments include the secreted protein as well as the mature form. Further preferred polypeptide fragments include the secreted protein or the mature form having a continuous series of deleted residues from the amino or the carboxy terminus, or both. For example, any number of amino acids, ranging from 1-60, can be deleted from the amino terminus of either the secreted polypeptide or the mature form. Similarly, any number of amino acids, ranging from 1-30, can be deleted from the carboxy terminus of the secreted protein or mature form.

Furthermore, any combination of the above amino and carboxy terminus deletions are preferred. Similarly, polynucleotides encoding these polypeptide fragments are also preferred.

**[0743]** Also preferred are polypeptide and polynucleotide fragments characterized by structural or functional domains, such as fragments that comprise alpha-helix and alpha-helix forming regions, beta-sheet and beta-sheet-forming regions, turn and turn-forming regions, coil and coil-forming regions, hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, flexible regions,

surface-forming regions, substrate binding region, and high antigenic index regions. Polypeptide fragments of SEQ ID NO:Y falling within conserved domains are specifically contemplated by the present invention. Moreover, polynucleotides encoding these domains are also contemplated.

**[0744]** Other preferred polypeptide fragments are biologically active fragments. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide of the present invention. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity. Polynucleotides encoding these polypeptide fragments are also encompassed by the invention.

**[0745]** Preferably, the polynucleotide fragments of the invention encode a polypeptide which demonstrates a functional activity. By a polypeptide demonstrating a "functional activity" is meant, a polypeptide capable of displaying one or more known functional activities associated with a full-length (complete) polypeptide of invention protein. Such functional activities include, but are not limited to, biological activity, antigenicity [ability to bind (or compete with a polypeptide of the invention for binding) to an antibody to the polypeptide of the invention], immunogenicity (ability to generate antibody which binds to a polypeptide of the invention), ability to form multimers with polypeptides of the invention, and ability to bind to a receptor or ligand for a polypeptide of the invention.

**[0746]** The functional activity of polypeptides of the invention, and fragments, variants derivatives, and analogs thereof, can be assayed by various methods.

**[0747]** For example, in one embodiment where one is assaying for the ability to bind or compete with full-length polypeptide of the invention for binding to an antibody of the polypeptide of the invention, various immunoassays known in the art can be used, including but not limited to, competitive and non-competitive assay systems using techniques such as radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels, for example), western blots, precipitation reactions, agglutination assays (e.g., gel agglutination assays,

hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, and immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

[0748] In another embodiment, where a ligand for a polypeptide of the invention identified, or the ability of a polypeptide fragment, variant or derivative of the invention to multimerize is being evaluated, binding can be assayed, e.g., by means well-known in the art, such as, for example, reducing and non-reducing gel chromatography, protein affinity chromatography, and affinity blotting. See generally, Phizicky, E., et al., 1995, *Microbiol. Rev.* 59:94-123. In another embodiment, physiological correlates of binding of a polypeptide of the invention to its substrates (signal transduction) can be assayed.

[0749] In addition, assays described herein (see Examples) and otherwise known in the art may routinely be applied to measure the ability of polypeptides of the invention and fragments, variants derivatives and analogs thereof to elicit related biological activity related to that of the polypeptide of the invention (either in vitro or in vivo). Other methods will be known to the skilled artisan and are within the scope of the invention.

#### **[0750] Epitopes and Antibodies**

[0751] The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID NO:Y, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in ATCC deposit No. Z or encoded by a polynucleotide that hybridizes to the complement of the sequence of SEQ ID NO:X or contained in ATCC deposit No. Z under stringent hybridization conditions or lower stringency hybridization conditions as defined supra. The present invention further encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the

invention (such as, for example, the sequence disclosed in SEQ ID NO:X), polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to the complementary strand under stringent hybridization conditions or lower stringency hybridization conditions defined supra.

**[0752]** The term “epitopes,” as used herein, refers to portions of a polypeptide having antigenic or immunogenic activity in an animal, preferably a mammal, and most preferably in a human. In a preferred embodiment, the present invention encompasses a polypeptide comprising an epitope, as well as the polynucleotide encoding this polypeptide. An “immunogenic epitope,” as used herein, is defined as a portion of a protein that elicits an antibody response in an animal, as determined by any method known in the art, for example, by the methods for generating antibodies described infra. (See, for example, Geysen et al., Proc. Natl. Acad. Sci. USA 81:3998- 4002 (1983)). The term “antigenic epitope,” as used herein, is defined as a portion of a protein to which an antibody can immunospecifically bind its antigen as determined by any method well known in the art, for example, by the immunoassays described herein. Immunospecific binding excludes non-specific binding but does not necessarily exclude cross- reactivity with other antigens. Antigenic epitopes need not necessarily be immunogenic.

**[0753]** Fragments which function as epitopes may be produced by any conventional means. (See, e.g., Houghten, Proc. Natl. Acad. Sci. USA 82:5131-5135 (1985), further described in U.S. Patent No. 4,631,211).

**[0754]** In the present invention, antigenic epitopes preferably contain a sequence of at least 4, at least 5, at least 6, at least 7, more preferably at least 8, at least 9, at least 10, at least 11, at least 12, at least 13, at least 14, at least 15, at least 20, at least 25, at least 30, at least 40, at least 50, and, most preferably, between about 15 to about 30 amino acids. Preferred polypeptides comprising immunogenic or antigenic epitopes are at least 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100 amino acid residues in length. Additional non-exclusive preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as portions thereof. Antigenic epitopes are useful, for example, to raise antibodies, including monoclonal antibodies,



that specifically bind the epitope. Preferred antigenic epitopes include the antigenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these antigenic epitopes. Antigenic epitopes can be used as the target molecules in immunoassays. (See, for instance, Wilson et al., Cell 37:767-778 (1984); Sutcliffe et al., Science 219:660-666 (1983)).

[0755] Similarly, immunogenic epitopes can be used, for example, to induce antibodies according to methods well known in the art. (See, for instance, Sutcliffe et al., supra; Wilson et al., supra; Chow et al., Proc. Natl. Acad. Sci. USA 82:910-914; and Bittle et al., J. Gen. Virol. 66:2347-2354 (1985). Preferred immunogenic epitopes include the immunogenic epitopes disclosed herein, as well as any combination of two, three, four, five or more of these immunogenic epitopes. The polypeptides comprising one or more immunogenic epitopes may be presented for eliciting an antibody response together with a carrier protein, such as an albumin, to an animal system (such as rabbit or mouse), or, if the polypeptide is of sufficient length (at least about 25 amino acids), the polypeptide may be presented without a carrier. However, immunogenic epitopes comprising as few as 8 to 10 amino acids have been shown to be sufficient to raise antibodies capable of binding to, at the very least, linear epitopes in a denatured polypeptide (e.g., in Western blotting).

[0756] Epitope-bearing polypeptides of the present invention may be used to induce antibodies according to methods well known in the art including, but not limited to, in vivo immunization, in vitro immunization, and phage display methods. See, e.g., Sutcliffe et al., supra; Wilson et al., supra, and Bittle et al., J. Gen. Virol., 66:2347-2354 (1985). If in vivo immunization is used, animals may be immunized with free peptide; however, anti-peptide antibody titer may be boosted by coupling the peptide to a macromolecular carrier, such as keyhole limpet hemacyanin (KLH) or tetanus toxoid. For instance, peptides containing cysteine residues may be coupled to a carrier using a linker such as maleimidobenzoyl- N-hydroxysuccinimide ester (MBS), while other peptides may be coupled to carriers using a more general linking agent such as glutaraldehyde. Animals such as rabbits, rats and mice are immunized with either free or carrier- coupled peptides, for instance, by intraperitoneal and/or intradermal injection of emulsions containing about 100  $\mu$ g of peptide or carrier

protein and Freund's adjuvant or any other adjuvant known for stimulating an immune response. Several booster injections may be needed, for instance, at intervals of about two weeks, to provide a useful titer of anti-peptide antibody which can be detected, for example, by ELISA assay using free peptide adsorbed to a solid surface. The titer of anti-peptide antibodies in serum from an immunized animal may be increased by selection of anti-peptide antibodies, for instance, by adsorption to the peptide on a solid support and elution of the selected antibodies according to methods well known in the art.

**[0757]** As one of skill in the art will appreciate, and as discussed above, the polypeptides of the present invention comprising an immunogenic or antigenic epitope can be fused to other polypeptide sequences. For example, the polypeptides of the present invention may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof) resulting in chimeric polypeptides. Such fusion proteins may facilitate purification and may increase half-life in vivo. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker et al., *Nature*, 331:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion disulfide bonds have also been found to be more efficient in binding and neutralizing other molecules than monomeric polypeptides or fragments thereof alone. See, e.g., Fountoulakis et al., *J. Biochem.*, 270:3958-3964 (1995). Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin ("HA") tag or flag tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht et al. allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht et al., 1991, *Proc. Natl. Acad. Sci. USA* 88:8972- 897). In this system, the gene of interest is

subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni<sup>2+</sup>-nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

**[0758]** Additional fusion proteins of the invention may be generated through the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling"). DNA shuffling may be employed to modulate the activities of polypeptides of the invention, such methods can be used to generate polypeptides with altered activity, as well as agonists and antagonists of the polypeptides. See, generally, U.S. Patent Nos. 5,605,793; 5,811,238; 5,830,721; 5,834,252; and 5,837,458, and Patten et al., *Curr. Opinion Biotechnol.* 8:724-33 (1997); Harayama, *Trends Biotechnol.* 16(2):76-82 (1998); Hansson, et al., *J. Mol. Biol.* 287:265-76 (1999); and Lorenzo and Blasco, *Biotechniques* 24(2):308-13 (1998) (each of these patents and publications are hereby incorporated by reference in its entirety). In one embodiment, alteration of polynucleotides corresponding to SEQ ID NO:X and the polypeptides encoded by these polynucleotides may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments by homologous or site-specific recombination to generate variation in the polynucleotide sequence. In another embodiment, polynucleotides of the invention, or the encoded polypeptides, may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of a polynucleotide encoding a polypeptide of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules.

**[0759]** Antibodies

**[0760]** Further polypeptides of the invention relate to antibodies and T-cell antigen receptors (TCR) which immunospecifically bind a polypeptide, polypeptide fragment,

or variant of SEQ ID NO:Y, and/or an epitope, of the present invention (as determined by immunoassays well known in the art for assaying specific antibody-antigen binding). Antibodies of the invention include, but are not limited to, polyclonal, monoclonal, multispecific, human, humanized or chimeric antibodies, single chain antibodies, Fab fragments, F(ab') fragments, fragments produced by a Fab expression library, anti-idiotypic (anti-Id) antibodies (including, e.g., anti-Id antibodies to antibodies of the invention), and epitope-binding fragments of any of the above. The term "antibody," as used herein, refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, i.e., molecules that contain an antigen binding site that immunospecifically binds an antigen. The immunoglobulin molecules of the invention can be of any type (e.g., IgG, IgE, IgM, IgD, IgA and IgY), class (e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2) or subclass of immunoglobulin molecule.

[0761] Most preferably the antibodies are human antigen-binding antibody fragments of the present invention and include, but are not limited to, Fab, Fab' and F(ab')<sub>2</sub>, Fd, single-chain Fvs (scFv), single-chain antibodies, disulfide-linked Fvs (sdFv) and fragments comprising either a VL or VH domain. Antigen-binding antibody fragments, including single-chain antibodies, may comprise the variable region(s) alone or in combination with the entirety or a portion of the following: hinge region, CH1, CH2, and CH3 domains. Also included in the invention are antigen-binding fragments also comprising any combination of variable region(s) with a hinge region, CH1, CH2, and CH3 domains. The antibodies of the invention may be from any animal origin including birds and mammals. Preferably, the antibodies are human, murine (e.g., mouse and rat), donkey, ship rabbit, goat, guinea pig, camel, horse, or chicken. As used herein, "human" antibodies include antibodies having the amino acid sequence of a human immunoglobulin and include antibodies isolated from human immunoglobulin libraries or from animals transgenic for one or more human immunoglobulin and that do not express endogenous immunoglobulins, as described infra and, for example in, U.S. Patent No. 5,939,598 by Kucherlapati et al.

[0762] The antibodies of the present invention may be monospecific, bispecific, trispecific or of greater multispecificity. Multispecific antibodies may be specific for

different epitopes of a polypeptide of the present invention or may be specific for both a polypeptide of the present invention as well as for a heterologous epitope, such as a heterologous polypeptide or solid support material. See, e.g., PCT publications WO 93/17715; WO 92/08802; WO 91/00360; WO 92/05793; Tutt, et al., J. Immunol. 147:60-69 (1991); U.S. Patent Nos. 4,474,893; 4,714,681; 4,925,648; 5,573,920; 5,601,819; Kostelny et al., J. Immunol. 148:1547-1553 (1992).

**[0763]** Antibodies of the present invention may be described or specified in terms of the epitope(s) or portion(s) of a polypeptide of the present invention which they recognize or specifically bind. The epitope(s) or polypeptide portion(s) may be specified as described herein, e.g., by N-terminal and C-terminal positions, by size in contiguous amino acid residues, or listed in the Tables and Figures. Antibodies which specifically bind any epitope or polypeptide of the present invention may also be excluded. Therefore, the present invention includes antibodies that specifically bind polypeptides of the present invention, and allows for the exclusion of the same.

**[0764]** Antibodies of the present invention may also be described or specified in terms of their cross-reactivity. Antibodies that do not bind any other analog, ortholog, or homolog of a polypeptide of the present invention are included. Antibodies that bind polypeptides with at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 65%, at least 60%, at least 55%, and at least 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In specific embodiments, antibodies of the present invention cross-react with murine, rat and/or rabbit homologs of human proteins and the corresponding epitopes thereof. Antibodies that do not bind polypeptides with less than 95%, less than 90%, less than 85%, less than 80%, less than 75%, less than 70%, less than 65%, less than 60%, less than 55%, and less than 50% identity (as calculated using methods known in the art and described herein) to a polypeptide of the present invention are also included in the present invention. In a specific embodiment, the above-described cross-reactivity is with respect to any single specific antigenic or immunogenic polypeptide, or combination(s) of 2, 3, 4, 5, or more of the specific antigenic and/or immunogenic polypeptides disclosed herein. Further included in the

present invention are antibodies which bind polypeptides encoded by polynucleotides which hybridize to a polynucleotide of the present invention under stringent hybridization conditions (as described herein). Antibodies of the present invention may also be described or specified in terms of their binding affinity to a polypeptide of the invention. Preferred binding affinities include those with a dissociation constant or  $K_d$  less than  $5 \times 10^{-2}$  M,  $10^{-2}$  M,  $5 \times 10^{-3}$  M,  $10^{-3}$  M,  $5 \times 10^{-4}$  M,  $10^{-4}$  M,  $5 \times 10^{-5}$  M,  $10^{-5}$  M,  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M,  $10^{-8}$  M,  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M,  $10^{-13}$  M,  $5 \times 10^{-14}$  M,  $10^{-14}$  M,  $5 \times 10^{-15}$  M, or  $10^{-15}$  M.

[0765] The invention also provides antibodies that competitively inhibit binding of an antibody to an epitope of the invention as determined by any method known in the art for determining competitive binding, for example, the immunoassays described herein. In preferred embodiments, the antibody competitively inhibits binding to the epitope by at least 95%, at least 90%, at least 85 %, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50%.

[0766] Antibodies of the present invention may act as agonists or antagonists of the polypeptides of the present invention. For example, the present invention includes antibodies which disrupt the receptor/ligand interactions with the polypeptides of the invention either partially or fully. Preferably, antibodies of the present invention bind an antigenic epitope disclosed herein, or a portion thereof. The invention features both receptor-specific antibodies and ligand-specific antibodies. The invention also features receptor-specific antibodies which do not prevent ligand binding but prevent receptor activation. Receptor activation (i.e., signaling) may be determined by techniques described herein or otherwise known in the art. For example, receptor activation can be determined by detecting the phosphorylation (e.g., tyrosine or serine/threonine) of the receptor or its substrate by immunoprecipitation followed by western blot analysis (for example, as described supra). In specific embodiments, antibodies are provided that inhibit ligand activity or receptor activity by at least 95%, at least 90%, at least 85%, at least 80%, at least 75%, at least 70%, at least 60%, or at least 50% of the activity in absence of the antibody.

**[0767]** The invention also features receptor-specific antibodies which both prevent ligand binding and receptor activation as well as antibodies that recognize the receptor-ligand complex, and, preferably, do not specifically recognize the unbound receptor or the unbound ligand. Likewise, included in the invention are neutralizing antibodies which bind the ligand and prevent binding of the ligand to the receptor, as well as antibodies which bind the ligand, thereby preventing receptor activation, but do not prevent the ligand from binding the receptor. Further included in the invention are antibodies which activate the receptor. These antibodies may act as receptor agonists, i.e., potentiate or activate either all or a subset of the biological activities of the ligand-mediated receptor activation, for example, by inducing dimerization of the receptor. The antibodies may be specified as agonists, antagonists or inverse agonists for biological activities comprising the specific biological activities of the peptides of the invention disclosed herein. The above antibody agonists can be made using methods known in the art. See, e.g., PCT publication WO 96/40281; U.S. Patent No. 5,811,097; Deng et al., *Blood* 92(6):1981-1988 (1998); Chen et al., *Cancer Res.* 58(16):3668-3678 (1998); Harrop et al., *J. Immunol.* 161(4):1786-1794 (1998); Zhu et al., *Cancer Res.* 58(15):3209-3214 (1998); Yoon et al., *J. Immunol.* 160(7):3170-3179 (1998); Prat et al., *J. Cell. Sci.* 111(Pt2):237-247 (1998); Pitard et al., *J. Immunol. Methods* 205(2):177-190 (1997); Liautard et al., *Cytokine* 9(4):233-241 (1997); Carlson et al., *J. Biol. Chem.* 272(17):11295-11301 (1997); Taryman et al., *Neuron* 14(4):755-762 (1995); Muller et al., *Structure* 6(9):1153-1167 (1998); Bartunek et al., *Cytokine* 8(1):14-20 (1996) (which are all incorporated by reference herein in their entireties).

**[0768]** Antibodies of the present invention may be used, for example, but not limited to, to purify, detect, and target the polypeptides of the present invention, including both in vitro and in vivo diagnostic and therapeutic methods. For example, the antibodies have use in immunoassays for qualitatively and quantitatively measuring levels of the polypeptides of the present invention in biological samples. See, e.g., Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988) (incorporated by reference herein in its entirety).

[0769] As discussed in more detail below, the antibodies of the present invention may be used either alone or in combination with other compositions. The antibodies may further be recombinantly fused to a heterologous polypeptide at the N- or C-terminus or chemically conjugated (including covalently and non-covalently conjugations) to polypeptides or other compositions. For example, antibodies of the present invention may be recombinantly fused or conjugated to molecules useful as labels in detection assays and effector molecules such as heterologous polypeptides, drugs, radionuclides, or toxins. See, e.g., PCT publications WO 92/08495; WO 91/14438; WO 89/12624; U.S. Patent No. 5,314,995; and EP 396,387.

[0770] The antibodies of the invention include derivatives that are modified, i.e., by the covalent attachment of any type of molecule to the antibody such that covalent attachment does not prevent the antibody from generating an anti-idiotypic response. For example, but not by way of limitation, the antibody derivatives include antibodies that have been modified, e.g., by glycosylation, acetylation, pegylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to a cellular ligand or other protein, etc. Any of numerous chemical modifications may be carried out by known techniques, including, but not limited to specific chemical cleavage, acetylation, formylation, metabolic synthesis of tunicamycin, etc. Additionally, the derivative may contain one or more non-classical amino acids.

[0771] The antibodies of the present invention may be generated by any suitable method known in the art. Polyclonal antibodies to an antigen-of-interest can be produced by various procedures well known in the art. For example, a polypeptide of the invention can be administered to various host animals including, but not limited to, rabbits, mice, rats, etc. to induce the production of sera containing polyclonal antibodies specific for the antigen. Various adjuvants may be used to increase the immunological response, depending on the host species, and include but are not limited to, Freund's (complete and incomplete), mineral gels such as aluminum hydroxide, surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanins, dinitrophenol, and



potentially useful human adjuvants such as BCG (bacille Calmette-Guerin) and corynebacterium parvum. Such adjuvants are also well known in the art.

[0772] Monoclonal antibodies can be prepared using a wide variety of techniques known in the art including the use of hybridoma, recombinant, and phage display technologies, or a combination thereof. For example, monoclonal antibodies can be produced using hybridoma techniques including those known in the art and taught, for example, in Harlow et al., *Antibodies: A Laboratory Manual*, (Cold Spring Harbor Laboratory Press, 2nd ed. 1988); Hammerling, et al., in: *Monoclonal Antibodies and T-Cell Hybridomas* 563-681 (Elsevier, N.Y., 1981) (said references incorporated by reference in their entireties). The term “monoclonal antibody” as used herein is not limited to antibodies produced through hybridoma technology. The term “monoclonal antibody” refers to an antibody that is derived from a single clone, including any eukaryotic, prokaryotic, or phage clone, and not the method by which it is produced.

[0773] Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art and are discussed in detail in the Examples (e.g., Example 16). In a non-limiting example, mice can be immunized with a polypeptide of the invention or a cell expressing such peptide. Once an immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

[0774] Accordingly, the present invention provides methods of generating monoclonal antibodies as well as antibodies produced by the method comprising culturing a hybridoma cell secreting an antibody of the invention wherein, preferably, the hybridoma is generated by fusing splenocytes isolated from a mouse immunized with an antigen of the invention with myeloma cells and then screening the

hybridomas resulting from the fusion for hybridoma clones that secrete an antibody able to bind a polypeptide of the invention.

[0775] Antibody fragments which recognize specific epitopes may be generated by known techniques. For example, Fab and F(ab')<sub>2</sub> fragments of the invention may be produced by proteolytic cleavage of immunoglobulin molecules, using enzymes such as papain (to produce Fab fragments) or pepsin (to produce F(ab')<sub>2</sub> fragments).

F(ab')<sub>2</sub> fragments contain the variable region, the light chain constant region and the CH1 domain of the heavy chain.

[0776] For example, the antibodies of the present invention can also be generated using various phage display methods known in the art. In phage display methods, functional antibody domains are displayed on the surface of phage particles which carry the polynucleotide sequences encoding them. In a particular embodiment, such phage can be utilized to display antigen binding domains expressed from a repertoire or combinatorial antibody library (e.g., human or murine). Phage expressing an antigen binding domain that binds the antigen of interest can be selected or identified with antigen, e.g., using labeled antigen or antigen bound or captured to a solid surface or bead. Phage used in these methods are typically filamentous phage including fd and M13 binding domains expressed from phage with Fab, Fv or disulfide stabilized Fv antibody domains recombinantly fused to either the phage gene III or gene VIII protein. Examples of phage display methods that can be used to make the antibodies of the present invention include those disclosed in Brinkman et al., *J. Immunol. Methods* 182:41-50 (1995); Ames et al., *J. Immunol. Methods* 184:177-186 (1995); Kettleborough et al., *Eur. J. Immunol.* 24:952-958 (1994); Persic et al., *Gene* 187 9-18 (1997); Burton et al., *Advances in Immunology* 57:191-280 (1994); PCT application No. PCT/GB91/01134; PCT publications WO 90/02809; WO 91/10737; WO 92/01047; WO 92/18619; WO 93/11236; WO 95/15982; WO 95/20401; and U.S. Patent Nos. 5,698,426; 5,223,409; 5,403,484; 5,580,717; 5,427,908; 5,750,753; 5,821,047; 5,571,698; 5,427,908; 5,516,637; 5,780,225; 5,658,727; 5,733,743 and 5,969,108; each of which is incorporated herein by reference in its entirety.

[0777] As described in the above references, after phage selection, the antibody coding regions from the phage can be isolated and used to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host, including mammalian cells, insect cells, plant cells, yeast, and bacteria, e.g., as described in detail below. For example, techniques to recombinantly produce Fab, Fab' and F(ab')<sub>2</sub> fragments can also be employed using methods known in the art such as those disclosed in PCT publication WO 92/22324; Mullinax et al., *BioTechniques* 12(6):864-869 (1992); and Sawai et al., *AJRI* 34:26-34 (1995); and Better et al., *Science* 240:1041-1043 (1988) (said references incorporated by reference in their entirety).

[0778] Examples of techniques which can be used to produce single-chain Fvs and antibodies include those described in U.S. Patents 4,946,778 and 5,258,498; Huston et al., *Methods in Enzymology* 203:46-88 (1991); Shu et al., *PNAS* 90:7995-7999 (1993); and Skerra et al., *Science* 240:1038-1040 (1988). For some uses, including in vivo use of antibodies in humans and in vitro detection assays, it may be preferable to use chimeric, humanized, or human antibodies. A chimeric antibody is a molecule in which different portions of the antibody are derived from different animal species, such as antibodies having a variable region derived from a murine monoclonal antibody and a human immunoglobulin constant region. Methods for producing chimeric antibodies are known in the art. See e.g., Morrison, *Science* 229:1202 (1985); Oi et al., *BioTechniques* 4:214 (1986); Gillies et al., (1989) *J. Immunol. Methods* 125:191-202; U.S. Patent Nos. 5,807,715; 4,816,567; and 4,816,397, which are incorporated herein by reference in their entirety. Humanized antibodies are antibody molecules from non-human species antibody that binds the desired antigen having one or more complementarity determining regions (CDRs) from the non-human species and a framework regions from a human immunoglobulin molecule. Often, framework residues in the human framework regions will be substituted with the corresponding residue from the CDR donor antibody to alter, preferably improve, antigen binding. These framework substitutions are identified by methods well known in the art, e.g., by modeling of the interactions of the CDR and framework residues to identify framework residues important for antigen binding and sequence

comparison to identify unusual framework residues at particular positions. (See, e.g., Queen et al., U.S. Patent No. 5,585,089; Riechmann et al., *Nature* 332:323 (1988), which are incorporated herein by reference in their entireties.) Antibodies can be humanized using a variety of techniques known in the art including, for example, CDR-grafting (EP 239,400; PCT publication WO 91/09967; U.S. Patent Nos. 5,225,539; 5,530,101; and 5,585,089), veneering or resurfacing (EP 592,106; EP 519,596; Padlan, *Molecular Immunology* 28(4/5):489-498 (1991); Studnicka et al., *Protein Engineering* 7(6):805-814 (1994); Roguska et al., *PNAS* 91:969-973 (1994)), and chain shuffling (U.S. Patent No. 5,565,332).

**[0779]** Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Human antibodies can be made by a variety of methods known in the art including phage display methods described above using antibody libraries derived from human immunoglobulin sequences. See also, U.S. Patent Nos. 4,444,887 and 4,716,111; and PCT publications WO 98/46645, WO 98/50433, WO 98/24893, WO 98/16654, WO 96/34096, WO 96/33735, and WO 91/10741; each of which is incorporated herein by reference in its entirety.

**[0780]** Human antibodies can also be produced using transgenic mice which are incapable of expressing functional endogenous immunoglobulins, but which can express human immunoglobulin genes. For example, the human heavy and light chain immunoglobulin gene complexes may be introduced randomly or by homologous recombination into mouse embryonic stem cells. Alternatively, the human variable region, constant region, and diversity region may be introduced into mouse embryonic stem cells in addition to the human heavy and light chain genes. The mouse heavy and light chain immunoglobulin genes may be rendered non-functional separately or simultaneously with the introduction of human immunoglobulin loci by homologous recombination. In particular, homozygous deletion of the JH region prevents endogenous antibody production. The modified embryonic stem cells are expanded and microinjected into blastocysts to produce chimeric mice. The chimeric mice are then bred to produce homozygous offspring which express human antibodies. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention.

Monoclonal antibodies directed against the antigen can be obtained from the immunized, transgenic mice using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA, IgM and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, *Int. Rev. Immunol.* 13:65-93 (1995). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., PCT publications WO 98/24893; WO 92/01047; WO 96/34096; WO 96/33735; European Patent No. 0 598 877; U.S. Patent Nos. 5,413,923; 5,625,126; 5,633,425; 5,569,825; 5,661,016; 5,545,806; 5,814,318; 5,885,793; 5,916,771; and 5,939,598, which are incorporated by reference herein in their entirety. In addition, companies such as Abgenix, Inc. (Freemont, CA) and Genpharm (San Jose, CA) can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

**[0781]** Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a mouse antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., *Bio/technology* 12:899-903 (1988)).

**[0782]** Further, antibodies to the polypeptides of the invention can, in turn, be utilized to generate anti-idiotypic antibodies that "mimic" polypeptides of the invention using techniques well known to those skilled in the art. (See, e.g., Greenspan & Bona, *FASEB J.* 7(5):437-444; (1989) and Nissinoff, J. *Immunol.* 147(8):2429-2438 (1991)). For example, antibodies which bind to and competitively inhibit polypeptide multimerization and/or binding of a polypeptide of the invention to a ligand can be used to generate anti-idiotypes that "mimic" the polypeptide multimerization and/or binding domain and, as a consequence, bind to and neutralize polypeptide and/or its ligand. Such neutralizing anti-idiotypes or Fab fragments of such anti-idiotypes can be used in therapeutic regimens to neutralize polypeptide ligand. For example, such

anti-idiotypic antibodies can be used to bind a polypeptide of the invention and/or to bind its ligands/receptors, and thereby block its biological activity.

**[0783] Polynucleotides Encoding Antibodies**

**[0784]** The invention further provides polynucleotides comprising a nucleotide sequence encoding an antibody of the invention and fragments thereof. The invention also encompasses polynucleotides that hybridize under stringent or lower stringency hybridization conditions, e.g., as defined supra, to polynucleotides that encode an antibody, preferably, that specifically binds to a polypeptide of the invention, preferably, an antibody that binds to a polypeptide having the amino acid sequence of SEQ ID NO:Y.

**[0785]** The polynucleotides may be obtained, and the nucleotide sequence of the polynucleotides determined, by any method known in the art. For example, if the nucleotide sequence of the antibody is known, a polynucleotide encoding the antibody may be assembled from chemically synthesized oligonucleotides (e.g., as described in Kutmeier et al., BioTechniques 17:242 (1994)), which, briefly, involves the synthesis of overlapping oligonucleotides containing portions of the sequence encoding the antibody, annealing and ligating of those oligonucleotides, and then amplification of the ligated oligonucleotides by PCR.

**[0786]** Alternatively, a polynucleotide encoding an antibody may be generated from nucleic acid from a suitable source. If a clone containing a nucleic acid encoding a particular antibody is not available, but the sequence of the antibody molecule is known, a nucleic acid encoding the immunoglobulin may be chemically synthesized or obtained from a suitable source (e.g., an antibody cDNA library, or a cDNA library generated from, or nucleic acid, preferably poly A<sup>+</sup> RNA, isolated from, any tissue or cells expressing the antibody, such as hybridoma cells selected to express an antibody of the invention) by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of the sequence or by cloning using an oligonucleotide probe specific for the particular gene sequence to identify, e.g., a cDNA clone from a cDNA library that encodes the antibody. Amplified nucleic acids generated by PCR

may then be cloned into replicable cloning vectors using any method well known in the art.

[0787] Once the nucleotide sequence and corresponding amino acid sequence of the antibody is determined, the nucleotide sequence of the antibody may be manipulated using methods well known in the art for the manipulation of nucleotide sequences, e.g., recombinant DNA techniques, site directed mutagenesis, PCR, etc. (see, for example, the techniques described in Sambrook et al., 1990, *Molecular Cloning, A Laboratory Manual*, 2d Ed., Cold Spring Harbor Laboratory, Cold Spring Harbor, NY and Ausubel et al., eds., 1998, *Current Protocols in Molecular Biology*, John Wiley & Sons, NY, which are both incorporated by reference herein in their entireties), to generate antibodies having a different amino acid sequence, for example to create amino acid substitutions, deletions, and/or insertions.

[0788] In a specific embodiment, the amino acid sequence of the heavy and/or light chain variable domains may be inspected to identify the sequences of the complementarity determining regions (CDRs) by methods that are well known in the art, e.g., by comparison to known amino acid sequences of other heavy and light chain variable regions to determine the regions of sequence hypervariability. Using routine recombinant DNA techniques, one or more of the CDRs may be inserted within framework regions, e.g., into human framework regions to humanize a non-human antibody, as described supra. The framework regions may be naturally occurring or consensus framework regions, and preferably human framework regions (see, e.g., Chothia et al., *J. Mol. Biol.* 278: 457-479 (1998) for a listing of human framework regions). Preferably, the polynucleotide generated by the combination of the framework regions and CDRs encodes an antibody that specifically binds a polypeptide of the invention. Preferably, as discussed supra, one or more amino acid substitutions may be made within the framework regions, and, preferably, the amino acid substitutions improve binding of the antibody to its antigen. Additionally, such methods may be used to make amino acid substitutions or deletions of one or more variable region cysteine residues participating in an intrachain disulfide bond to generate antibody molecules lacking one or more intrachain disulfide bonds. Other

alterations to the polynucleotide are encompassed by the present invention and within the skill of the art.

**[0789]** In addition, techniques developed for the production of "chimeric antibodies" (Morrison et al., Proc. Natl. Acad. Sci. 81:851-855 (1984); Neuberger et al., Nature 312:604-608 (1984); Takeda et al., Nature 314:452-454 (1985)) by splicing genes from a mouse antibody molecule of appropriate antigen specificity together with genes from a human antibody molecule of appropriate biological activity can be used. As described supra, a chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region, e.g., humanized antibodies.

**[0790]** Alternatively, techniques described for the production of single chain antibodies (U.S. Patent No. 4,946,778; Bird, Science 242:423- 42 (1988); Huston et al., Proc. Natl. Acad. Sci. USA 85:5879-5883 (1988); and Ward et al., Nature 334:544-54 (1989)) can be adapted to produce single chain antibodies. Single chain antibodies are formed by linking the heavy and light chain fragments of the Fv region via an amino acid bridge, resulting in a single chain polypeptide. Techniques for the assembly of functional Fv fragments in E. coli may also be used (Skerra et al., Science 242:1038- 1041 (1988)).

#### **[0791] Methods of Producing Antibodies**

**[0792]** The antibodies of the invention can be produced by any method known in the art for the synthesis of antibodies, in particular, by chemical synthesis or preferably, by recombinant expression techniques.

**[0793]** Recombinant expression of an antibody of the invention, or fragment, derivative or analog thereof, (e.g., a heavy or light chain of an antibody of the invention or a single chain antibody of the invention), requires construction of an expression vector containing a polynucleotide that encodes the antibody. Once a polynucleotide encoding an antibody molecule or a heavy or light chain of an antibody, or portion thereof (preferably containing the heavy or light chain variable domain), of the invention has been obtained, the vector for the production of the



antibody molecule may be produced by recombinant DNA technology using techniques well known in the art. Thus, methods for preparing a protein by expressing a polynucleotide containing an antibody encoding nucleotide sequence are described herein. Methods which are well known to those skilled in the art can be used to construct expression vectors containing antibody coding sequences and appropriate transcriptional and translational control signals. These methods include, for example, in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. The invention, thus, provides replicable vectors comprising a nucleotide sequence encoding an antibody molecule of the invention, or a heavy or light chain thereof, or a heavy or light chain variable domain, operably linked to a promoter. Such vectors may include the nucleotide sequence encoding the constant region of the antibody molecule (see, e.g., PCT Publication WO 86/05807; PCT Publication WO 89/01036; and U.S. Patent No. 5,122,464) and the variable domain of the antibody may be cloned into such a vector for expression of the entire heavy or light chain.

**[0794]** The expression vector is transferred to a host cell by conventional techniques and the transfected cells are then cultured by conventional techniques to produce an antibody of the invention. Thus, the invention includes host cells containing a polynucleotide encoding an antibody of the invention, or a heavy or light chain thereof, or a single chain antibody of the invention, operably linked to a heterologous promoter. In preferred embodiments for the expression of double-chained antibodies, vectors encoding both the heavy and light chains may be co-expressed in the host cell for expression of the entire immunoglobulin molecule, as detailed below.

**[0795]** A variety of host-expression vector systems may be utilized to express the antibody molecules of the invention. Such host-expression systems represent vehicles by which the coding sequences of interest may be produced and subsequently purified, but also represent cells which may, when transformed or transfected with the appropriate nucleotide coding sequences, express an antibody molecule of the invention in situ. These include but are not limited to microorganisms such as bacteria (e.g., *E. coli*, *B. subtilis*) transformed with recombinant bacteriophage DNA, plasmid DNA or cosmid DNA expression vectors containing antibody coding

sequences; yeast (e.g., *Saccharomyces*, *Pichia*) transformed with recombinant yeast expression vectors containing antibody coding sequences; insect cell systems infected with recombinant virus expression vectors (e.g., baculovirus) containing antibody coding sequences; plant cell systems infected with recombinant virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or transformed with recombinant plasmid expression vectors (e.g., Ti plasmid) containing antibody coding sequences; or mammalian cell systems (e.g., COS, CHO, BHK, 293, 3T3 cells) harboring recombinant expression constructs containing promoters derived from the genome of mammalian cells (e.g., metallothionein promoter) or from mammalian viruses (e.g., the adenovirus late promoter; the vaccinia virus 7.5K promoter). Preferably, bacterial cells such as *Escherichia coli*, and more preferably, eukaryotic cells, especially for the expression of whole recombinant antibody molecule, are used for the expression of a recombinant antibody molecule. For example, mammalian cells such as Chinese hamster ovary cells (CHO), in conjunction with a vector such as the major intermediate early gene promoter element from human cytomegalovirus is an effective expression system for antibodies (Foecking et al., *Gene* 45:101 (1986); Cockett et al., *Bio/Technology* 8:2 (1990)).

[0796] In bacterial systems, a number of expression vectors may be advantageously selected depending upon the use intended for the antibody molecule being expressed. For example, when a large quantity of such a protein is to be produced, for the generation of pharmaceutical compositions of an antibody molecule, vectors which direct the expression of high levels of fusion protein products that are readily purified may be desirable. Such vectors include, but are not limited, to the *E. coli* expression vector pUR278 (Ruther et al., *EMBO J.* 2:1791 (1983)), in which the antibody coding sequence may be ligated individually into the vector in frame with the lac Z coding region so that a fusion protein is produced; pIN vectors (Inouye & Inouye, *Nucleic Acids Res.* 13:3101-3109 (1985); Van Heeke & Schuster, *J. Biol. Chem.* 24:5503-5509 (1989)); and the like. pGEX vectors may also be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption

and binding to matrix glutathione-agarose beads followed by elution in the presence of free glutathione. The pGEX vectors are designed to include thrombin or factor Xa protease cleavage sites so that the cloned target gene product can be released from the GST moiety.

[0797] In an insect system, *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes. The virus grows in *Spodoptera frugiperda* cells. The antibody coding sequence may be cloned individually into non-essential regions (for example the polyhedrin gene) of the virus and placed under control of an AcNPV promoter (for example the polyhedrin promoter).

[0798] In mammalian host cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, the antibody coding sequence of interest may be ligated to an adenovirus transcription/translation control complex, e.g., the late promoter and tripartite leader sequence. This chimeric gene may then be inserted in the adenovirus genome by in vitro or in vivo recombination. Insertion in a non-essential region of the viral genome (e.g., region E1 or E3) will result in a recombinant virus that is viable and capable of expressing the antibody molecule in infected hosts. (e.g., see Logan & Shenk, Proc. Natl. Acad. Sci. USA 81:355-359 (1984)). Specific initiation signals may also be required for efficient translation of inserted antibody coding sequences. These signals include the ATG initiation codon and adjacent sequences. Furthermore, the initiation codon must be in phase with the reading frame of the desired coding sequence to ensure translation of the entire insert. These exogenous translational control signals and initiation codons can be of a variety of origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of appropriate transcription enhancer elements, transcription terminators, etc. (see Bittner et al., Methods in Enzymol. 153:51-544 (1987)).

[0799] In addition, a host cell strain may be chosen which modulates the expression of the inserted sequences, or modifies and processes the gene product in the specific fashion desired. Such modifications (e.g., glycosylation) and processing (e.g., cleavage) of protein products may be important for the function of the protein.

Different host cells have characteristic and specific mechanisms for the post-translational processing and modification of proteins and gene products. Appropriate cell lines or host systems can be chosen to ensure the correct modification and processing of the foreign protein expressed. To this end, eukaryotic host cells which possess the cellular machinery for proper processing of the primary transcript, glycosylation, and phosphorylation of the gene product may be used. Such mammalian host cells include but are not limited to CHO, VERO, BHK, HeLa, COS, MDCK, 293, 3T3, WI38, and in particular, breast cancer cell lines such as, for example, BT483, Hs578T, HTB2, BT20 and T47D, and normal mammary gland cell line such as, for example, CRL7030 and Hs578Bst.

**[0800]** For long-term, high-yield production of recombinant proteins, stable expression is preferred. For example, cell lines which stably express the antibody molecule may be engineered. Rather than using expression vectors which contain viral origins of replication, host cells can be transformed with DNA controlled by appropriate expression control elements (e.g., promoter, enhancer, sequences, transcription terminators, polyadenylation sites, etc.), and a selectable marker. Following the introduction of the foreign DNA, engineered cells may be allowed to grow for 1-2 days in an enriched media, and then are switched to a selective media. The selectable marker in the recombinant plasmid confers resistance to the selection and allows cells to stably integrate the plasmid into their chromosomes and grow to form foci which in turn can be cloned and expanded into cell lines. This method may advantageously be used to engineer cell lines which express the antibody molecule. Such engineered cell lines may be particularly useful in screening and evaluation of compounds that interact directly or indirectly with the antibody molecule.

**[0801]** A number of selection systems may be used, including but not limited to the herpes simplex virus thymidine kinase (Wigler et al., Cell 11:223 (1977)), hypoxanthine-guanine phosphoribosyltransferase (Szybalska & Szybalski, Proc. Natl. Acad. Sci. USA 48:202 (1992)), and adenine phosphoribosyltransferase (Lowy et al., Cell 22:817 (1980)) genes can be employed in tk-, hgp<sup>r</sup>t- or ap<sup>r</sup>t- cells, respectively. Also, antimetabolite resistance can be used as the basis of selection for the following genes: dhfr, which confers resistance to methotrexate (Wigler et al., Natl. Acad. Sci.

USA 77:357 (1980); O'Hare et al., Proc. Natl. Acad. Sci. USA 78:1527 (1981)); gpt, which confers resistance to mycophenolic acid (Mulligan & Berg, Proc. Natl. Acad. Sci. USA 78:2072 (1981)); neo, which confers resistance to the aminoglycoside G-418 Clinical Pharmacy 12:488-505; Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217 (1993); May, 1993, TIB TECH 11(5):155-215); and hygro, which confers resistance to hygromycin (Santerre et al., Gene 30:147 (1984)). Methods commonly known in the art of recombinant DNA technology may be routinely applied to select the desired recombinant clone, and such methods are described, for example, in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990); and in Chapters 12 and 13, Dracopoli et al. (eds), Current Protocols in Human Genetics, John Wiley & Sons, NY (1994); Colberre-Garapin et al., J. Mol. Biol. 150:1 (1981), which are incorporated by reference herein in their entireties.

**[0802]** The expression levels of an antibody molecule can be increased by vector amplification (for a review, see Bebbington and Hentschel, The use of vectors based on gene amplification for the expression of cloned genes in mammalian cells in DNA cloning, Vol.3. (Academic Press, New York, 1987)). When a marker in the vector system expressing antibody is amplifiable, increase in the level of inhibitor present in culture of host cell will increase the number of copies of the marker gene. Since the amplified region is associated with the antibody gene, production of the antibody will also increase (Crouse et al., Mol. Cell. Biol. 3:257 (1983)).

**[0803]** The host cell may be co-transfected with two expression vectors of the invention, the first vector encoding a heavy chain derived polypeptide and the second vector encoding a light chain derived polypeptide. The two vectors may contain identical selectable markers which enable equal expression of heavy and light chain polypeptides. Alternatively, a single vector may be used which encodes, and is capable of expressing, both heavy and light chain polypeptides. In such situations, the light chain should be placed before the heavy chain to avoid an excess of toxic free heavy chain (Proudfoot, Nature 322:52 (1986); Kohler, Proc. Natl. Acad. Sci.

USA 77:2197 (1980)). The coding sequences for the heavy and light chains may comprise cDNA or genomic DNA.

**[0804]** Once an antibody molecule of the invention has been produced by an animal, chemically synthesized, or recombinantly expressed, it may be purified by any method known in the art for purification of an immunoglobulin molecule, for example, by chromatography (e.g., ion exchange, affinity, particularly by affinity for the specific antigen after Protein A, and sizing column chromatography), centrifugation, differential solubility, or by any other standard technique for the purification of proteins. In addition, the antibodies of the present invention or fragments thereof can be fused to heterologous polypeptide sequences described herein or otherwise known in the art, to facilitate purification.

**[0805]** The present invention encompasses antibodies recombinantly fused or chemically conjugated (including both covalently and non-covalently conjugations) to a polypeptide (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention to generate fusion proteins. The fusion does not necessarily need to be direct, but may occur through linker sequences. The antibodies may be specific for antigens other than polypeptides (or portion thereof, preferably at least 10, 20, 30, 40, 50, 60, 70, 80, 90 or 100 amino acids of the polypeptide) of the present invention. For example, antibodies may be used to target the polypeptides of the present invention to particular cell types, either in vitro or in vivo, by fusing or conjugating the polypeptides of the present invention to antibodies specific for particular cell surface receptors. Antibodies fused or conjugated to the polypeptides of the present invention may also be used in in vitro immunoassays and purification methods using methods known in the art. See e.g., Harbor et al., supra, and PCT publication WO 93/21232; EP 439,095; Naramura et al., Immunol. Lett. 39:91-99 (1994); U.S. Patent 5,474,981; Gillies et al., PNAS 89:1428-1432 (1992); Fell et al., J. Immunol. 146:2446-2452(1991), which are incorporated by reference in their entireties.

**[0806]** The present invention further includes compositions comprising the polypeptides of the present invention fused or conjugated to antibody domains other than the variable regions. For example, the polypeptides of the present invention may

be fused or conjugated to an antibody Fc region, or portion thereof. The antibody portion fused to a polypeptide of the present invention may comprise the constant region, hinge region, CH1 domain, CH2 domain, and CH3 domain or any combination of whole domains or portions thereof. The polypeptides may also be fused or conjugated to the above antibody portions to form multimers. For example, Fc portions fused to the polypeptides of the present invention can form dimers through disulfide bonding between the Fc portions. Higher multimeric forms can be made by fusing the polypeptides to portions of IgA and IgM. Methods for fusing or conjugating the polypeptides of the present invention to antibody portions are known in the art. See, e.g., U.S. Patent Nos. 5,336,603; 5,622,929; 5,359,046; 5,349,053; 5,447,851; 5,112,946; EP 307,434; EP 367,166; PCT publications WO 96/04388; WO 91/06570; Ashkenazi et al., Proc. Natl. Acad. Sci. USA 88:10535-10539 (1991); Zheng et al., J. Immunol. 154:5590-5600 (1995); and Vil et al., Proc. Natl. Acad. Sci. USA 89:11337-11341 (1992) (said references incorporated by reference in their entireties).

[0807] As discussed, supra, the polypeptides corresponding to a polypeptide, polypeptide fragment, or a variant of SEQ ID NO:Y may be fused or conjugated to the above antibody portions to increase the in vivo half life of the polypeptides or for use in immunoassays using methods known in the art. Further, the polypeptides corresponding to SEQ ID NO:Y may be fused or conjugated to the above antibody portions to facilitate purification. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP 394,827; Traunecker et al., Nature 331:84-86 (1988)). The polypeptides of the present invention fused or conjugated to an antibody having disulfide-linked dimeric structures (due to the IgG) may also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., J. Biochem. 270:3958-3964 (1995)). In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP A 232,262). Alternatively, deleting the Fc part after the fusion protein has been

expressed, detected, and purified, would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, Bennett et al., *J. Molecular Recognition* 8:52-58 (1995); Johanson et al., *J. Biol. Chem.* 270:9459-9471 (1995).

**[0808]** Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., *Proc. Natl. Acad. Sci. USA* 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson et al., *Cell* 37:767 (1984)) and the "flag" tag.

**[0809]** The present invention further encompasses antibodies or fragments thereof conjugated to a diagnostic or therapeutic agent. The antibodies can be used diagnostically to, for example, monitor the development or progression of a tumor as part of a clinical testing procedure to, e.g., determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive materials, positron emitting metals using various positron emission tomographies, and nonradioactive paramagnetic metal ions. The detectable substance may be coupled or conjugated either directly to the antibody (or fragment thereof) or indirectly, through an intermediate (such as, for example, a linker known in the art) using techniques known in the art. See, for example, U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics according to the present invention. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase;



examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin, and aequorin; and examples of suitable radioactive material include  $^{125}\text{I}$ ,  $^{131}\text{I}$ ,  $^{111}\text{In}$  or  $^{99}\text{Tc}$ .

[0810] Further, an antibody or fragment thereof may be conjugated to a therapeutic moiety such as a cytotoxin, e.g., a cytostatic or cytocidal agent, a therapeutic agent or a radioactive metal ion, e.g., alpha-emitters such as, for example,  $^{213}\text{Bi}$ . A cytotoxin or cytotoxic agent includes any agent that is detrimental to cells. Examples include paclitaxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, teniposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof. Therapeutic agents include, but are not limited to, antimetabolites (e.g., methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (e.g., mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclophosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (e.g., daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (e.g., dactinomycin (formerly actinomycin), bleomycin, mithramycin, and anthramycin (AMC)), and anti-mitotic agents (e.g., vincristine and vinblastine).

[0811] The conjugates of the invention can be used for modifying a given biological response, the therapeutic agent or drug moiety is not to be construed as limited to classical chemical therapeutic agents. For example, the drug moiety may be a protein or polypeptide possessing a desired biological activity. Such proteins may include, for example, a toxin such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin; a protein such as tumor necrosis factor,  $\alpha$ -interferon,  $\beta$ -interferon, nerve growth factor, platelet derived growth factor, tissue plasminogen activator, an apoptotic

agent, e.g., TNF-alpha, TNF-beta, AIM I (See, International Publication No. WO 97/33899), AIM II (See, International Publication No. WO 97/34911), Fas Ligand (Takahashi *et al.*, *Int. Immunol.*, 6:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a thrombotic agent or an anti- angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"), interleukin-2 ("IL-2"), interleukin-6 ("IL-6"), granulocyte macrophage colony stimulating factor ("GM-CSF"), granulocyte colony stimulating factor ("G-CSF"), or other growth factors.

**[0812]** Antibodies may also be attached to solid supports, which are particularly useful for immunoassays or purification of the target antigen. Such solid supports include, but are not limited to, glass, cellulose, polyacrylamide, nylon, polystyrene, polyvinyl chloride or polypropylene.

**[0813]** Techniques for conjugating such therapeutic moiety to antibodies are well known, see, e.g., Arnon *et al.*, "Monoclonal Antibodies For Immunotargeting Of Drugs In Cancer Therapy", in *Monoclonal Antibodies And Cancer Therapy*, Reisfeld *et al.* (eds.), pp. 243-56 (Alan R. Liss, Inc. 1985); Hellstrom *et al.*, "Antibodies For Drug Delivery", in *Controlled Drug Delivery* (2nd Ed.), Robinson *et al.* (eds.), pp. 623-53 (Marcel Dekker, Inc. 1987); Thorpe, "Antibody Carriers Of Cytotoxic Agents In Cancer Therapy: A Review", in *Monoclonal Antibodies '84: Biological And Clinical Applications*, Pinchera *et al.* (eds.), pp. 475-506 (1985); "Analysis, Results, And Future Prospective Of The Therapeutic Use Of Radiolabeled Antibody In Cancer Therapy", in *Monoclonal Antibodies For Cancer Detection And Therapy*, Baldwin *et al.* (eds.), pp. 303-16 (Academic Press 1985), and Thorpe *et al.*, "The Preparation And Cytotoxic Properties Of Antibody-Toxin Conjugates", *Immunol. Rev.* 62:119-58 (1982).

**[0814]** Alternatively, an antibody can be conjugated to a second antibody to form an antibody heteroconjugate as described by Segal in U.S. Patent No. 4,676,980, which is incorporated herein by reference in its entirety.

**[0815]** An antibody, with or without a therapeutic moiety conjugated to it, administered alone or in combination with cytotoxic factor(s) and/or cytokine(s) can be used as a therapeutic.

**[0816] Immunophenotyping**

**[0817]** The antibodies of the invention may be utilized for immunophenotyping of cell lines and biological samples. The translation product of the gene of the present invention may be useful as a cell specific marker, or more specifically as a cellular marker that is differentially expressed at various stages of differentiation and/or maturation of particular cell types. Monoclonal antibodies directed against a specific epitope, or combination of epitopes, will allow for the screening of cellular populations expressing the marker. Various techniques can be utilized using monoclonal antibodies to screen for cellular populations expressing the marker(s), and include magnetic separation using antibody-coated magnetic beads, "panning" with antibody attached to a solid matrix (i.e., plate), and flow cytometry (See, e.g., U.S. Patent 5,985,660; and Morrison *et al.*, *Cell*, 96:737-49 (1999)).

**[0818]** These techniques allow for the screening of particular populations of cells, such as might be found with hematological malignancies (i.e. minimal residual disease (MRD) in acute leukemic patients) and "non-self" cells in transplantations to prevent Graft-versus-Host Disease (GVHD). Alternatively, these techniques allow for the screening of hematopoietic stem and progenitor cells capable of undergoing proliferation and/or differentiation, as might be found in human umbilical cord blood.

**[0819] Assays For Antibody Binding**

**[0820]** The antibodies of the invention may be assayed for immunospecific binding by any method known in the art. The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few. Such assays are routine and well known in the art (see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York, which is incorporated by

reference herein in its entirety). Exemplary immunoassays are described briefly below (but are not intended by way of limitation).

**[0821]** Immunoprecipitation protocols generally comprise lysing a population of cells in a lysis buffer such as RIPA buffer (1% NP-40 or Triton X-100, 1% sodium deoxycholate, 0.1% SDS, 0.15 M NaCl, 0.01 M sodium phosphate at pH 7.2, 1% Trasyolol) supplemented with protein phosphatase and/or protease inhibitors (e.g., EDTA, PMSF, aprotinin, sodium vanadate), adding the antibody of interest to the cell lysate, incubating for a period of time (e.g., 1-4 hours) at 4° C, adding protein A and/or protein G sepharose beads to the cell lysate, incubating for about an hour or more at 4° C, washing the beads in lysis buffer and resuspending the beads in SDS/sample buffer. The ability of the antibody of interest to immunoprecipitate a particular antigen can be assessed by, e.g., western blot analysis. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the binding of the antibody to an antigen and decrease the background (e.g., pre-clearing the cell lysate with sepharose beads). For further discussion regarding immunoprecipitation protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.16.1.

**[0822]** Western blot analysis generally comprises preparing protein samples, electrophoresis of the protein samples in a polyacrylamide gel (e.g., 8%-20% SDS-PAGE depending on the molecular weight of the antigen), transferring the protein sample from the polyacrylamide gel to a membrane such as nitrocellulose, PVDF or nylon, blocking the membrane in blocking solution (e.g., PBS with 3% BSA or non-fat milk), washing the membrane in washing buffer (e.g., PBS-Tween 20), blocking the membrane with primary antibody (the antibody of interest) diluted in blocking buffer, washing the membrane in washing buffer, blocking the membrane with a secondary antibody (which recognizes the primary antibody, e.g., an anti-human antibody) conjugated to an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) or radioactive molecule (e.g., <sup>32</sup>P or <sup>125</sup>I) diluted in blocking buffer, washing the membrane in wash buffer, and detecting the presence of the antigen. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected and to reduce the background noise. For

further discussion regarding western blot protocols see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 10.8.1.

**[0823]** ELISAs comprise preparing antigen, coating the well of a 96 well microtiter plate with the antigen, adding the antibody of interest conjugated to a detectable compound such as an enzymatic substrate (e.g., horseradish peroxidase or alkaline phosphatase) to the well and incubating for a period of time, and detecting the presence of the antigen. In ELISAs the antibody of interest does not have to be conjugated to a detectable compound; instead, a second antibody (which recognizes the antibody of interest) conjugated to a detectable compound may be added to the well. Further, instead of coating the well with the antigen, the antibody may be coated to the well. In this case, a second antibody conjugated to a detectable compound may be added following the addition of the antigen of interest to the coated well. One of skill in the art would be knowledgeable as to the parameters that can be modified to increase the signal detected as well as other variations of ELISAs known in the art. For further discussion regarding ELISAs see, e.g., Ausubel et al, eds, 1994, Current Protocols in Molecular Biology, Vol. 1, John Wiley & Sons, Inc., New York at 11.2.1.

**[0824]** The binding affinity of an antibody to an antigen and the off-rate of an antibody-antigen interaction can be determined by competitive binding assays. One example of a competitive binding assay is a radioimmunoassay comprising the incubation of labeled antigen (e.g., <sup>3</sup>H or <sup>125</sup>I) with the antibody of interest in the presence of increasing amounts of unlabeled antigen, and the detection of the antibody bound to the labeled antigen. The affinity of the antibody of interest for a particular antigen and the binding off-rates can be determined from the data by scatchard plot analysis. Competition with a second antibody can also be determined using radioimmunoassays. In this case, the antigen is incubated with antibody of interest conjugated to a labeled compound (e.g., <sup>3</sup>H or <sup>125</sup>I) in the presence of increasing amounts of an unlabeled second antibody.

**[0825]** Therapeutic Uses

**[0826]** The present invention is further directed to antibody-based therapies which involve administering antibodies of the invention to an animal, preferably a mammal, and most preferably a human, patient for treating one or more of the disclosed diseases, disorders, or conditions. Therapeutic compounds of the invention include, but are not limited to, antibodies of the invention (including fragments, analogs and derivatives thereof as described herein) and nucleic acids encoding antibodies of the invention (including fragments, analogs and derivatives thereof and anti-idiotypic antibodies as described herein). The antibodies of the invention can be used to treat, inhibit or prevent diseases, disorders or conditions associated with aberrant expression and/or activity of a polypeptide of the invention, including, but not limited to, any one or more of the diseases, disorders, or conditions described herein. The treatment and/or prevention of diseases, disorders, or conditions associated with aberrant expression and/or activity of a polypeptide of the invention includes, but is not limited to, alleviating symptoms associated with those diseases, disorders or conditions. Antibodies of the invention may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

**[0827]** A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

**[0828]** The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors (such as, e.g., IL-2, IL-3 and IL-7), for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

**[0829]** The antibodies of the invention may be administered alone or in combination with other types of treatments (e.g., radiation therapy, chemotherapy, hormonal

therapy, immunotherapy and anti-tumor agents). Generally, administration of products of a species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, human antibodies, fragments derivatives, analogs, or nucleic acids, are administered to a human patient for therapy or prophylaxis.

**[0830]** It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of disorders related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides of the invention, including fragments thereof. Preferred binding affinities include those with a dissociation constant or  $K_d$  less than  $5 \times 10^{-2}$  M,  $10^{-2}$  M,  $5 \times 10^{-3}$  M,  $10^{-3}$  M,  $5 \times 10^{-4}$  M,  $10^{-4}$  M,  $5 \times 10^{-5}$  M,  $10^{-5}$  M,  $5 \times 10^{-6}$  M,  $10^{-6}$  M,  $5 \times 10^{-7}$  M,  $10^{-7}$  M,  $5 \times 10^{-8}$  M,  $10^{-8}$  M,  $5 \times 10^{-9}$  M,  $10^{-9}$  M,  $5 \times 10^{-10}$  M,  $10^{-10}$  M,  $5 \times 10^{-11}$  M,  $10^{-11}$  M,  $5 \times 10^{-12}$  M,  $10^{-12}$  M,  $5 \times 10^{-13}$  M,  $10^{-13}$  M,  $5 \times 10^{-14}$  M,  $10^{-14}$  M,  $5 \times 10^{-15}$  M, and  $10^{-15}$  M.

**[0831]** Gene Therapy

**[0832]** In a specific embodiment, nucleic acids comprising sequences encoding antibodies or functional derivatives thereof, are administered to treat, inhibit or prevent a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention, by way of gene therapy. Gene therapy refers to therapy performed by the administration to a subject of an expressed or expressible nucleic acid. In this embodiment of the invention, the nucleic acids produce their encoded protein that mediates a therapeutic effect.

**[0833]** Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

**[0834]** For general reviews of the methods of gene therapy, see Goldspiel et al., Clinical Pharmacy 12:488-505 (1993); Wu and Wu, Biotherapy 3:87-95 (1991); Tolstoshev, Ann. Rev. Pharmacol. Toxicol. 32:573-596 (1993); Mulligan, Science 260:926-932 (1993); and Morgan and Anderson, Ann. Rev. Biochem. 62:191-217

(1993); May, TIBTECH 11(5):155-215 (1993). Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), Current Protocols in Molecular Biology, John Wiley & Sons, NY (1993); and Kriegler, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY (1990).

**[0835]** In a preferred aspect, the compound comprises nucleic acid sequences encoding an antibody, said nucleic acid sequences being part of expression vectors that express the antibody or fragments or chimeric proteins or heavy or light chains thereof in a suitable host. In particular, such nucleic acid sequences have promoters operably linked to the antibody coding region, said promoter being inducible or constitutive, and, optionally, tissue- specific. In another particular embodiment, nucleic acid molecules are used in which the antibody coding sequences and any other desired sequences are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intrachromosomal expression of the antibody encoding nucleic acids (Koller and Smithies, Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); Zijlstra et al., Nature 342:435-438 (1989). In specific embodiments, the expressed antibody molecule is a single chain antibody; alternatively, the nucleic acid sequences include sequences encoding both the heavy and light chains, or fragments thereof, of the antibody.

**[0836]** Delivery of the nucleic acids into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid- carrying vectors, or indirect, in which case, cells are first transformed with the nucleic acids in vitro, then transplanted into the patient. These two approaches are known, respectively, as in vivo or ex vivo gene therapy.

**[0837]** In a specific embodiment, the nucleic acid sequences are directly administered in vivo, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing them as part of an appropriate nucleic acid expression vector and administering it so that they become intracellular, e.g., by infection using defective or attenuated retrovirals or other viral vectors (see U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun;



Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, encapsulation in liposomes, microparticles, or microcapsules, or by administering them in linkage to a peptide which is known to enter the nucleus, by administering it in linkage to a ligand subject to receptor-mediated endocytosis (see, e.g., Wu and Wu, *J. Biol. Chem.* 262:4429-4432 (1987)) (which can be used to target cell types specifically expressing the receptors), etc. In another embodiment, nucleic acid-ligand complexes can be formed in which the ligand comprises a fusogenic viral peptide to disrupt endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted *in vivo* for cell specific uptake and expression, by targeting a specific receptor (see, e.g., PCT Publications WO 92/06180; WO 92/22635; WO92/20316; WO93/14188, WO 93/20221). Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, *Proc. Natl. Acad. Sci. USA* 86:8932-8935 (1989); Zijlstra et al., *Nature* 342:435-438 (1989)).

**[0838]** In a specific embodiment, viral vectors that contains nucleic acid sequences encoding an antibody of the invention are used. For example, a retroviral vector can be used (see Miller et al., *Meth. Enzymol.* 217:581-599 (1993)). These retroviral vectors contain the components necessary for the correct packaging of the viral genome and integration into the host cell DNA. The nucleic acid sequences encoding the antibody to be used in gene therapy are cloned into one or more vectors, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., *Biotherapy* 6:291-302 (1994), which describes the use of a retroviral vector to deliver the *mdr1* gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are: Clowes et al., *J. Clin. Invest.* 93:644-651 (1994); Kiem et al., *Blood* 83:1467-1473 (1994); Salmons and Gunzberg, *Human Gene Therapy* 4:129-141 (1993); and Grossman and Wilson, *Curr. Opin. in Genetics and Devel.* 3:110-114 (1993).

**[0839]** Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory

epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are liver, the central nervous system, endothelial cells, and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, *Current Opinion in Genetics and Development* 3:499-503 (1993) present a review of adenovirus-based gene therapy. Bout et al., *Human Gene Therapy* 5:3-10 (1994) demonstrated the use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., *Science* 252:431-434 (1991); Rosenfeld et al., *Cell* 68:143-155 (1992); Mastrangeli et al., *J. Clin. Invest.* 91:225-234 (1993); PCT Publication WO94/12649; and Wang, et al., *Gene Therapy* 2:775-783 (1995). In a preferred embodiment, adenovirus vectors are used.

**[0840]** Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., *Proc. Soc. Exp. Biol. Med.* 204:289-300 (1993); U.S. Patent No. 5,436,146).

**[0841]** Another approach to gene therapy involves transferring a gene to cells in tissue culture by such methods as electroporation, lipofection, calcium phosphate mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene. Those cells are then delivered to a patient.

**[0842]** In this embodiment, the nucleic acid is introduced into a cell prior to administration in vivo of the resulting recombinant cell. Such introduction can be carried out by any method known in the art, including but not limited to transfection, electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, *Meth. Enzymol.* 217:599-618 (1993); Cohen et al., *Meth. Enzymol.* 217:618-644 (1993); Cline, *Pharmac. Ther.* 29:69-92m (1985) and may be used in accordance with the present invention, provided that the necessary

developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably heritable and expressible by its cell progeny.

**[0843]** The resulting recombinant cells can be delivered to a patient by various methods known in the art. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

**[0844]** Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes; blood cells such as Tlymphocytes, Blymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, granulocytes; various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

**[0845]** In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

**[0846]** In an embodiment in which recombinant cells are used in gene therapy, nucleic acid sequences encoding an antibody are introduced into the cells such that they are expressible by the cells or their progeny, and the recombinant cells are then administered in vivo for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained in vitro can potentially be used in accordance with this embodiment of the present invention (see e.g. PCT Publication WO 94/08598; Stemple and Anderson, Cell 71:973-985 (1992); Rheinwald, Meth. Cell Bio. 21A:229 (1980); and Pittelkow and Scott, Mayo Clinic Proc. 61:771 (1986)).

**[0847]** In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by controlling the presence or

absence of the appropriate inducer of transcription. Demonstration of Therapeutic or Prophylactic Activity

**[0848]** The compounds or pharmaceutical compositions of the invention are preferably tested in vitro, and then in vivo for the desired therapeutic or prophylactic activity, prior to use in humans. For example, in vitro assays to demonstrate the therapeutic or prophylactic utility of a compound or pharmaceutical composition include, the effect of a compound on a cell line or a patient tissue sample. The effect of the compound or composition on the cell line and/or tissue sample can be determined utilizing techniques known to those of skill in the art including, but not limited to, rosette formation assays and cell lysis assays. In accordance with the invention, in vitro assays which can be used to determine whether administration of a specific compound is indicated, include in vitro cell culture assays in which a patient tissue sample is grown in culture, and exposed to or otherwise administered a compound, and the effect of such compound upon the tissue sample is observed.

**[0849]** Therapeutic/Prophylactic Administration and Composition

**[0850]** The invention provides methods of treatment, inhibition and prophylaxis by administration to a subject of an effective amount of a compound or pharmaceutical composition of the invention, preferably an antibody of the invention. In a preferred aspect, the compound is substantially purified (e.g., substantially free from substances that limit its effect or produce undesired side-effects). The subject is preferably an animal, including but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human.

**[0851]** Formulations and methods of administration that can be employed when the compound comprises a nucleic acid or an immunoglobulin are described above; additional appropriate formulations and routes of administration can be selected from among those described herein below.

**[0852]** Various delivery systems are known and can be used to administer a compound of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the compound, receptor-mediated endocytosis (see, e.g., Wu and Wu, J. Biol. Chem. 262:4429-4432 (1987)),

construction of a nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds or compositions may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compounds or compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

**[0853]** In a specific embodiment, it may be desirable to administer the pharmaceutical compounds or compositions of the invention locally to the area in need of treatment; this may be achieved by, for example, and not by way of limitation, local infusion during surgery, topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. Preferably, when administering a protein, including an antibody, of the invention, care must be taken to use materials to which the protein does not absorb.

**[0854]** In another embodiment, the compound or composition can be delivered in a vesicle, in particular a liposome (see Langer, *Science* 249:1527-1533 (1990); Treat et al., in *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler (eds.), Liss, New York, pp. 353- 365 (1989); Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*)

**[0855]** In yet another embodiment, the compound or composition can be delivered in a controlled release system. In one embodiment, a pump may be used (see Langer, *supra*; Sefton, *CRC Crit. Ref. Biomed. Eng.* 14:201 (1987); Buchwald et al., *Surgery* 88:507 (1980); Saudek et al., *N. Engl. J. Med.* 321:574 (1989)). In another

embodiment, polymeric materials can be used (see Medical Applications of Controlled Release, Langer and Wise (eds.), CRC Pres., Boca Raton, Florida (1974); Controlled Drug Bioavailability, Drug Product Design and Performance, Smolen and Ball (eds.), Wiley, New York (1984); Ranger and Peppas, J., Macromol. Sci. Rev. Macromol. Chem. 23:61 (1983); see also Levy et al., Science 228:190 (1985); During et al., Ann. Neurol. 25:351 (1989); Howard et al., J.Neurosurg. 71:105 (1989)). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (see, e.g., Goodson, in Medical Applications of Controlled Release, supra, vol. 2, pp. 115-138 (1984)).

**[0856]** Other controlled release systems are discussed in the review by Langer (Science 249:1527-1533 (1990)).

**[0857]** In a specific embodiment where the compound of the invention is a nucleic acid encoding a protein, the nucleic acid can be administered in vivo to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (see U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or coating with lipids or cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (see e.g., Joliot et al., Proc. Natl. Acad. Sci. USA 88:1864-1868 (1991)), etc. Alternatively, a nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination.

**[0858]** The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a compound, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water

and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions can also be employed as liquid carriers, particularly for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsion, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the compound, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

**[0859]** In a preferred embodiment, the composition is formulated in accordance with routine procedures as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lignocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition

is administered by injection, an ampoule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

**[0860]** The compounds of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with anions such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with cations such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

**[0861]** The amount of the compound of the invention which will be effective in the treatment, inhibition and prevention of a disease or disorder associated with aberrant expression and/or activity of a polypeptide of the invention can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

**[0862]** For antibodies, the dosage administered to a patient is typically 0.1 mg/kg to 100 mg/kg of the patient's body weight. Preferably, the dosage administered to a patient is between 0.1 mg/kg and 20 mg/kg of the patient's body weight, more preferably 1 mg/kg to 10 mg/kg of the patient's body weight. Generally, human antibodies have a longer half-life within the human body than antibodies from other species due to the immune response to the foreign polypeptides. Thus, lower dosages of human antibodies and less frequent administration is often possible. Further, the dosage and frequency of administration of antibodies of the invention may be reduced by enhancing uptake and tissue penetration (e.g., into the brain) of the antibodies by modifications such as, for example, lipidation.

**[0863]** The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture,



use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

**[0864] Diagnosis and Imaging**

**[0865]** Labeled antibodies, and derivatives and analogs thereof, which specifically bind to a polypeptide of interest can be used for diagnostic purposes to detect, diagnose, or monitor diseases, disorders, and/or conditions associated with the aberrant expression and/or activity of a polypeptide of the invention. The invention provides for the detection of aberrant expression of a polypeptide of interest, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of aberrant expression.

**[0866]** The invention provides a diagnostic assay for diagnosing a disorder, comprising (a) assaying the expression of the polypeptide of interest in cells or body fluid of an individual using one or more antibodies specific to the polypeptide interest and (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a particular disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

**[0867]** Antibodies of the invention can be used to assay protein levels in a biological sample using classical immunohistological methods known to those of skill in the art (e.g., see Jalkanen, et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, et al., J. Cell Biol. 105:3087-3096 (1987)). Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody

assay labels are known in the art and include enzyme labels, such as, glucose oxidase; radioisotopes, such as iodine ( $^{125}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{112}\text{In}$ ), and technetium ( $^{99}\text{Tc}$ ); luminescent labels, such as luminol; and fluorescent labels, such as fluorescein and rhodamine, and biotin.

**[0868]** One aspect of the invention is the detection and diagnosis of a disease or disorder associated with aberrant expression of a polypeptide of interest in an animal, preferably a mammal and most preferably a human. In one embodiment, diagnosis comprises: a) administering (for example, parenterally, subcutaneously, or intraperitoneally) to a subject an effective amount of a labeled molecule which specifically binds to the polypeptide of interest; b) waiting for a time interval following the administering for permitting the labeled molecule to preferentially concentrate at sites in the subject where the polypeptide is expressed (and for unbound labeled molecule to be cleared to background level); c) determining background level; and d) detecting the labeled molecule in the subject, such that detection of labeled molecule above the background level indicates that the subject has a particular disease or disorder associated with aberrant expression of the polypeptide of interest. Background level can be determined by various methods including, comparing the amount of labeled molecule detected to a standard value previously determined for a particular system.

**[0869]** It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of  $^{99\text{m}}\text{Tc}$ . The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in *Tumor Imaging: The Radiochemical Detection of Cancer*, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).

**[0870]** Depending on several variables, including the type of label used and the mode of administration, the time interval following the administration for permitting the

labeled molecule to preferentially concentrate at sites in the subject and for unbound labeled molecule to be cleared to background level is 6 to 48 hours or 6 to 24 hours or 6 to 12 hours. In another embodiment the time interval following administration is 5 to 20 days or 5 to 10 days.

[0871] In an embodiment, monitoring of the disease or disorder is carried out by repeating the method for diagnosing the disease or disease, for example, one month after initial diagnosis, six months after initial diagnosis, one year after initial diagnosis, etc.

[0872] Presence of the labeled molecule can be detected in the patient using methods known in the art for in vivo scanning. These methods depend upon the type of label used. Skilled artisans will be able to determine the appropriate method for detecting a particular label. Methods and devices that may be used in the diagnostic methods of the invention include, but are not limited to, computed tomography (CT), whole body scan such as position emission tomography (PET), magnetic resonance imaging (MRI), and sonography.

[0873] In a specific embodiment, the molecule is labeled with a radioisotope and is detected in the patient using a radiation responsive surgical instrument (Thurston et al., U.S. Patent No. 5,441,050). In another embodiment, the molecule is labeled with a fluorescent compound and is detected in the patient using a fluorescence responsive scanning instrument. In another embodiment, the molecule is labeled with a positron emitting metal and is detected in the patient using positron emission-tomography. In yet another embodiment, the molecule is labeled with a paramagnetic label and is detected in a patient using magnetic resonance imaging (MRI).

[0874] Kits

[0875] The present invention provides kits that can be used in the above methods. In one embodiment, a kit comprises an antibody of the invention, preferably a purified antibody, in one or more containers. In a specific embodiment, the kits of the present invention contain a substantially isolated polypeptide comprising an epitope which is specifically immunoreactive with an antibody included in the kit. Preferably, the kits of the present invention further comprise a control antibody which does not react with the polypeptide of interest. In another specific embodiment, the kits of the present

invention contain a means for detecting the binding of an antibody to a polypeptide of interest (e.g., the antibody may be conjugated to a detectable substrate such as a fluorescent compound, an enzymatic substrate, a radioactive compound or a luminescent compound, or a second antibody which recognizes the first antibody may be conjugated to a detectable substrate).

**[0876]** In another specific embodiment of the present invention, the kit is a diagnostic kit for use in screening serum containing antibodies specific against proliferative and/or cancerous polynucleotides and polypeptides. Such a kit may include a control antibody that does not react with the polypeptide of interest. Such a kit may include a substantially isolated polypeptide antigen comprising an epitope which is specifically immunoreactive with at least one anti-polypeptide antigen antibody. Further, such a kit includes means for detecting the binding of said antibody to the antigen (e.g., the antibody may be conjugated to a fluorescent compound such as fluorescein or rhodamine which can be detected by flow cytometry). In specific embodiments, the kit may include a recombinantly produced or chemically synthesized polypeptide antigen. The polypeptide antigen of the kit may also be attached to a solid support.

**[0877]** In a more specific embodiment the detecting means of the above-described kit includes a solid support to which said polypeptide antigen is attached. Such a kit may also include a non-attached reporter-labeled anti-human antibody. In this embodiment, binding of the antibody to the polypeptide antigen can be detected by binding of the said reporter-labeled antibody.

**[0878]** In an additional embodiment, the invention includes a diagnostic kit for use in screening serum containing antigens of the polypeptide of the invention. The diagnostic kit includes a substantially isolated antibody specifically immunoreactive with polypeptide or polynucleotide antigens, and means for detecting the binding of the polynucleotide or polypeptide antigen to the antibody. In one embodiment, the antibody is attached to a solid support. In a specific embodiment, the antibody may be a monoclonal antibody. The detecting means of the kit may include a second, labeled monoclonal antibody. Alternatively, or in addition, the detecting means may include a labeled, competing antigen.

[0879] In one diagnostic configuration, test serum is reacted with a solid phase reagent having a surface-bound antigen obtained by the methods of the present invention. After binding with specific antigen antibody to the reagent and removing unbound serum components by washing, the reagent is reacted with reporter-labeled anti-human antibody to bind reporter to the reagent in proportion to the amount of bound anti-antigen antibody on the solid support. The reagent is again washed to remove unbound labeled antibody, and the amount of reporter associated with the reagent is determined. Typically, the reporter is an enzyme which is detected by incubating the solid phase in the presence of a suitable fluorometric, luminescent or colorimetric substrate (Sigma, St. Louis, MO).

[0880] The solid surface reagent in the above assay is prepared by known techniques for attaching protein material to solid support material, such as polymeric beads, dip sticks, 96-well plate or filter material. These attachment methods generally include non-specific adsorption of the protein to the support or covalent attachment of the protein, typically through a free amine group, to a chemically reactive group on the solid support, such as an activated carboxyl, hydroxyl, or aldehyde group. Alternatively, streptavidin coated plates can be used in conjunction with biotinylated antigen(s).

[0881] Thus, the invention provides an assay system or kit for carrying out this diagnostic method. The kit generally includes a support with surface-bound recombinant antigens, and a reporter-labeled anti-human antibody for detecting surface-bound anti-antigen antibody.

**[0882] Fusion Proteins**

[0883] Any polypeptide of the present invention can be used to generate fusion proteins. For example, the polypeptide of the present invention, when fused to a second protein, can be used as an antigenic tag. Antibodies raised against the polypeptide of the present invention can be used to indirectly detect the second protein by binding to the polypeptide. Moreover, because secreted proteins target cellular locations based on trafficking signals, the polypeptides of the present invention can be used as targeting molecules once fused to other proteins.

**[0884]** Examples of domains that can be fused to polypeptides of the present invention include not only heterologous signal sequences, but also other heterologous functional regions. The fusion does not necessarily need to be direct, but may occur through linker sequences.

**[0885]** Moreover, fusion proteins may also be engineered to improve characteristics of the polypeptide of the present invention. For instance, a region of additional amino acids, particularly charged amino acids, may be added to the N-terminus of the polypeptide to improve stability and persistence during purification from the host cell or subsequent handling and storage. Also, peptide moieties may be added to the polypeptide to facilitate purification. Such regions may be removed prior to final preparation of the polypeptide. The addition of peptide moieties to facilitate handling of polypeptides are familiar and routine techniques in the art.

**[0886]** Moreover, polypeptides of the present invention, including fragments, and specifically epitopes, can be combined with parts of the constant domain of immunoglobulins (IgA, IgE, IgG, IgM) or portions thereof (CH1, CH2, CH3, and any combination thereof, including both entire domains and portions thereof), resulting in chimeric polypeptides. These fusion proteins facilitate purification and show an increased half-life in vivo. One reported example describes chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. (EP A 394,827; Traunecker et al., *Nature* 331:84-86 (1988).) Fusion proteins having disulfide-linked dimeric structures (due to the IgG) can also be more efficient in binding and neutralizing other molecules, than the monomeric secreted protein or protein fragment alone. (Fountoulakis et al., *J. Biochem.* 270:3958-3964 (1995).)

**[0887]** Similarly, EP-A-O 464 533 (Canadian counterpart 2045869) discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, the Fc part in a fusion protein is beneficial in therapy and diagnosis, and thus can result in, for example, improved pharmacokinetic properties. (EP-A 0232 262.) Alternatively, deleting the Fc part after the fusion protein has been expressed, detected, and purified,

would be desired. For example, the Fc portion may hinder therapy and diagnosis if the fusion protein is used as an antigen for immunizations. In drug discovery, for example, human proteins, such as hIL-5, have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists of hIL-5. (See, D. Bennett et al., J. Molecular Recognition 8:52-58 (1995); K. Johanson et al., J. Biol. Chem. 270:9459-9471 (1995).)

[0888] Moreover, the polypeptides of the present invention can be fused to marker sequences, such as a peptide which facilitates purification of the fused polypeptide. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz et al., Proc. Natl. Acad. Sci. USA 86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Another peptide tag useful for purification, the "HA" tag, corresponds to an epitope derived from the influenza hemagglutinin protein. (Wilson et al., Cell 37:767 (1984).)

[0889] Thus, any of these above fusions can be engineered using the polynucleotides or the polypeptides of the present invention.

[0890] **Vectors, Host Cells, and Protein Production**

[0891] The present invention also relates to vectors containing the polynucleotide of the present invention, host cells, and the production of polypeptides by recombinant techniques. The vector may be, for example, a phage, plasmid, viral, or retroviral vector. Retroviral vectors may be replication competent or replication defective. In the latter case, viral propagation generally will occur only in complementing host cells.

[0892] The polynucleotides may be joined to a vector containing a selectable marker for propagation in a host. Generally, a plasmid vector is introduced in a precipitate, such as a calcium phosphate precipitate, or in a complex with a charged lipid. If the vector is a virus, it may be packaged in vitro using an appropriate packaging cell line and then transduced into host cells.

[0893] The polynucleotide insert should be operatively linked to an appropriate promoter, such as the phage lambda PL promoter, the *E. coli* lac, trp, phoA and tac promoters, the SV40 early and late promoters and promoters of retroviral LTRs, to name a few. Other suitable promoters will be known to the skilled artisan. The expression constructs will further contain sites for transcription initiation, termination, and, in the transcribed region, a ribosome binding site for translation. The coding portion of the transcripts expressed by the constructs will preferably include a translation initiating codon at the beginning and a termination codon (UAA, UGA or UAG) appropriately positioned at the end of the polypeptide to be translated.

[0894] As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells (e.g., *Saccharomyces cerevisiae* or *Pichia pastoris* (ATCC Accession No. 201178)); insect cells such as *Drosophila* S2 and *Spodoptera Sf9* cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

[0895] Among vectors preferred for use in bacteria include pQE70, pQE60 and pQE-9, available from QIAGEN, Inc.; pBluescript vectors, Phagescript vectors, pNH8A, pNH16a, pNH18A, pNH46A, available from Stratagene Cloning Systems, Inc.; and ptrc99a, pKK223-3, pKK233-3, pDR540, pRIT5 available from Pharmacia Biotech, Inc. Among preferred eukaryotic vectors are pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; and pSVK3, pBPV, pMSG and pSVL available from Pharmacia. Preferred expression vectors for use in yeast systems include, but are not limited to pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalph, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, pPIC9K, and PAO815 (all available from Invitrogen, Carlsbad, CA). Other suitable vectors will be readily apparent to the skilled artisan.



[0896] Introduction of the construct into the host cell can be effected by calcium phosphate transfection, DEAE-dextran mediated transfection, cationic lipid-mediated transfection, electroporation, transduction, infection, or other methods. Such methods are described in many standard laboratory manuals, such as Davis et al., Basic Methods In Molecular Biology (1986). It is specifically contemplated that the polypeptides of the present invention may in fact be expressed by a host cell lacking a recombinant vector.

[0897] A polypeptide of this invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography ("HPLC") is employed for purification.

[0898] Polypeptides of the present invention, and preferably the secreted form, can also be recovered from: products purified from natural sources, including bodily fluids, tissues and cells, whether directly isolated or cultured; products of chemical synthetic procedures; and products produced by recombinant techniques from a prokaryotic or eukaryotic host, including, for example, bacterial, yeast, higher plant, insect, and mammalian cells. Depending upon the host employed in a recombinant production procedure, the polypeptides of the present invention may be glycosylated or may be non-glycosylated. In addition, polypeptides of the invention may also include an initial modified methionine residue, in some cases as a result of host-mediated processes. Thus, it is well known in the art that the N-terminal methionine encoded by the translation initiation codon generally is removed with high efficiency from any protein after translation in all eukaryotic cells. While the N-terminal methionine on most proteins also is efficiently removed in most prokaryotes, for some proteins, this prokaryotic removal process is inefficient, depending on the nature of the amino acid to which the N-terminal methionine is covalently linked.

[0899] In one embodiment, the yeast *Pichia pastoris* is used to express the polypeptide of the present invention in a eukaryotic system. *Pichia pastoris* is a

methylophilic yeast which can metabolize methanol as its sole carbon source. A main step in the methanol metabolism pathway is the oxidation of methanol to formaldehyde using O<sub>2</sub>. This reaction is catalyzed by the enzyme alcohol oxidase. In order to metabolize methanol as its sole carbon source, *Pichia pastoris* must generate high levels of alcohol oxidase due, in part, to the relatively low affinity of alcohol oxidase for O<sub>2</sub>. Consequently, in a growth medium depending on methanol as a main carbon source, the promoter region of one of the two alcohol oxidase genes (*AOX1*) is highly active. In the presence of methanol, alcohol oxidase produced from the *AOX1* gene comprises up to approximately 30% of the total soluble protein in *Pichia pastoris*. See, Ellis, S.B., et al., *Mol. Cell. Biol.* 5:1111-21 (1985); Koutz, P.J., et al., *Yeast* 5:167-77 (1989); Tschopp, J.F., et al., *Nucl. Acids Res.* 15:3859-76 (1987). Thus, a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, under the transcriptional regulation of all or part of the *AOX1* regulatory sequence is expressed at exceptionally high levels in *Pichia* yeast grown in the presence of methanol.

**[0900]** In one example, the plasmid vector pPIC9K is used to express DNA encoding a polypeptide of the invention, as set forth herein, in a *Pichea* yeast system essentially as described in "*Pichia* Protocols: Methods in Molecular Biology," D.R. Higgins and J. Cregg, eds. The Humana Press, Totowa, NJ, 1998. This expression vector allows expression and secretion of a protein of the invention by virtue of the strong *AOX1* promoter linked to the *Pichia pastoris* alkaline phosphatase (PHO) secretory signal peptide (i.e., leader) located upstream of a multiple cloning site.

**[0901]** Many other yeast vectors could be used in place of pPIC9K, such as, pYES2, pYD1, pTEF1/Zeo, pYES2/GS, pPICZ, pGAPZ, pGAPZalpha, pPIC9, pPIC3.5, pHIL-D2, pHIL-S1, pPIC3.5K, and PAO815, as one skilled in the art would readily appreciate, as long as the proposed expression construct provides appropriately located signals for transcription, translation, secretion (if desired), and the like, including an in-frame AUG as required.

**[0902]** In another embodiment, high-level expression of a heterologous coding sequence, such as, for example, a polynucleotide of the present invention, may be achieved by cloning the heterologous polynucleotide of the invention into an expression vector such as, for example, pGAPZ or pGAPZalpha, and growing the yeast culture in the absence of methanol.

**[0903]** In addition to encompassing host cells containing the vector constructs discussed herein, the invention also encompasses primary, secondary, and immortalized host cells of vertebrate origin, particularly mammalian origin, that have been engineered to delete or replace endogenous genetic material (e.g., coding sequence), and/or to include genetic material (e.g., heterologous polynucleotide sequences) that is operably associated with the polynucleotides of the invention, and which activates, alters, and/or amplifies endogenous polynucleotides. For example, techniques known in the art may be used to operably associate heterologous control regions (e.g., promoter and/or enhancer) and endogenous polynucleotide sequences via homologous recombination, resulting in the formation of a new transcription unit (see, e.g., U.S. Patent No. 5,641,670, issued June 24, 1997; U.S. Patent No. 5,733,761, issued March 31, 1998; International Publication No. WO 96/29411, published September 26, 1996; International Publication No. WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA 86:8932-8935 (1989); and Zijlstra et al., Nature 342:435-438 (1989), the disclosures of each of which are incorporated by reference in their entireties).

**[0904]** In addition, polypeptides of the invention can be chemically synthesized using techniques known in the art (e.g., see Creighton, 1983, Proteins: Structures and Molecular Principles, W.H. Freeman & Co., N.Y., and Hunkapiller et al., *Nature*, 310:105-111 (1984)). For example, a polypeptide corresponding to a fragment of a polypeptide sequence of the invention can be synthesized by use of a peptide synthesizer. Furthermore, if desired, nonclassical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the polypeptide sequence. Non-classical amino acids include, but are not limited to, to the D-isomers of the common amino acids, 2,4-diaminobutyric acid,  $\alpha$ -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid, g-Abu, e-Ahx, 6-amino hexanoic acid,

Aib, 2-amino isobutyric acid, 3-amino propionic acid, ornithine, norleucine, norvaline, hydroxyproline, sarcosine, citrulline, homocitrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine, b-alanine, fluoro-amino acids, designer amino acids such as b-methyl amino acids, Ca-methyl amino acids, Na-methyl amino acids, and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

**[0905]** The invention encompasses polypeptides which are differentially modified during or after translation, *e.g.*, by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited, to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, NaBH<sub>4</sub>; acetylation, formylation, oxidation, reduction; metabolic synthesis in the presence of tunicamycin; etc.

**[0906]** Additional post-translational modifications encompassed by the invention include, for example, *e.g.*, N-linked or O-linked carbohydrate chains, processing of N-terminal or C-terminal ends), attachment of chemical moieties to the amino acid backbone, chemical modifications of N-linked or O-linked carbohydrate chains, and addition or deletion of an N-terminal methionine residue as a result of procaryotic host cell expression. The polypeptides may also be modified with a detectable label, such as an enzymatic, fluorescent, isotopic or affinity label to allow for detection and isolation of the protein.

**[0907]** Also provided by the invention are chemically modified derivatives of the polypeptides of the invention which may provide additional advantages such as increased solubility, stability and circulating time of the polypeptide, or decreased immunogenicity (see U.S. Patent NO: 4,179,337). The chemical moieties for derivitization may be selected from water soluble polymers such as polyethylene glycol, ethylene glycol/propylene glycol copolymers, carboxymethylcellulose, dextran, polyvinyl alcohol and the like. The polypeptides may be modified at random positions within the molecule, or at predetermined positions within the molecule and may include one, two, three or more attached chemical moieties.

**[0908]** The polymer may be of any molecular weight, and may be branched or unbranched. For polyethylene glycol, the preferred molecular weight is between about 1 kDa and about 100 kDa (the term "about" indicating that in preparations of polyethylene glycol, some molecules will weigh more, some less, than the stated molecular weight) for ease in handling and manufacturing. Other sizes may be used, depending on the desired therapeutic profile (e.g., the duration of sustained release desired, the effects, if any on biological activity, the ease in handling, the degree or lack of antigenicity and other known effects of the polyethylene glycol to a therapeutic protein or analog).

**[0909]** The polyethylene glycol molecules (or other chemical moieties) should be attached to the protein with consideration of effects on functional or antigenic domains of the protein. There are a number of attachment methods available to those skilled in the art, e.g., EP 0 401 384, herein incorporated by reference (coupling PEG to G-CSF), see also Malik et al., *Exp. Hematol.* 20:1028-1035 (1992) (reporting pegylation of GM-CSF using tresyl chloride). For example, polyethylene glycol may be covalently bound through amino acid residues via a reactive group, such as, a free amino or carboxyl group. Reactive groups are those to which an activated polyethylene glycol molecule may be bound. The amino acid residues having a free amino group may include lysine residues and the N-terminal amino acid residues; those having a free carboxyl group may include aspartic acid residues glutamic acid residues and the C-terminal amino acid residue. Sulfhydryl groups may also be used as a reactive group for attaching the polyethylene glycol molecules. Preferred for therapeutic purposes is attachment at an amino group, such as attachment at the N-terminus or lysine group.

**[0910]** One may specifically desire proteins chemically modified at the N-terminus. Using polyethylene glycol as an illustration of the present composition, one may select from a variety of polyethylene glycol molecules (by molecular weight, branching, etc.), the proportion of polyethylene glycol molecules to protein (polypeptide) molecules in the reaction mix, the type of pegylation reaction to be performed, and the method of obtaining the selected N-terminally pegylated protein. The method of obtaining the N-terminally pegylated preparation (i.e., separating this

moiety from other monopegylated moieties if necessary) may be by purification of the N-terminally pegylated material from a population of pegylated protein molecules. Selective proteins chemically modified at the N-terminus modification may be accomplished by reductive alkylation which exploits differential reactivity of different types of primary amino groups (lysine versus the N-terminal) available for derivatization in a particular protein. Under the appropriate reaction conditions, substantially selective derivatization of the protein at the N-terminus with a carbonyl group containing polymer is achieved.

[0911] The polypeptides of the invention may be in monomers or multimers (i.e., dimers, trimers, tetramers and higher multimers). Accordingly, the present invention relates to monomers and multimers of the polypeptides of the invention, their preparation, and compositions (preferably, *Therapeutics*) containing them. In specific embodiments, the polypeptides of the invention are monomers, dimers, trimers or tetramers. In additional embodiments, the multimers of the invention are at least dimers, at least trimers, or at least tetramers.

[0912] Multimers encompassed by the invention may be homomers or heteromers. As used herein, the term homomer, refers to a multimer containing only polypeptides corresponding to the amino acid sequence of SEQ ID NO:Y or encoded by the cDNA contained in a deposited clone (including fragments, variants, splice variants, and fusion proteins, corresponding to these polypeptides as described herein). These homomers may contain polypeptides having identical or different amino acid sequences. In a specific embodiment, a homomer of the invention is a multimer containing only polypeptides having an identical amino acid sequence. In another specific embodiment, a homomer of the invention is a multimer containing polypeptides having different amino acid sequences. In specific embodiments, the multimer of the invention is a homodimer (*e.g.*, containing polypeptides having identical or different amino acid sequences) or a homotrimer (*e.g.*, containing polypeptides having identical and/or different amino acid sequences). In additional embodiments, the homomeric multimer of the invention is at least a homodimer, at least a homotrimer, or at least a homotetramer.

**[0913]** As used herein, the term heteromer refers to a multimer containing one or more heterologous polypeptides (*i.e.*, polypeptides of different proteins) in addition to the polypeptides of the invention. In a specific embodiment, the multimer of the invention is a heterodimer, a heterotrimer, or a heterotetramer. In additional embodiments, the heteromeric multimer of the invention is at least a heterodimer, at least a heterotrimer, or at least a heterotetramer.

**[0914]** Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution. In another embodiment, heteromultimers of the invention, such as, for example, heterotrimers or heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in the sequence listing, or contained in the polypeptide encoded by a deposited clone). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (*i.e.*, naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a fusion protein of the invention.

**[0915]** In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in an Fc fusion protein of the invention (as described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from

another protein that is capable of forming covalently associated multimers, such as for example, osteopontin (see, e.g., International Publication NO: WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more polypeptides of the invention are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple polypeptides of the invention separated by peptide linkers may be produced using conventional recombinant DNA technology.

**[0916]** Another method for preparing multimer polypeptides of the invention involves use of polypeptides of the invention fused to a leucine zipper or isoleucine zipper polypeptide sequence. Leucine zipper and isoleucine zipper domains are polypeptides that promote multimerization of the proteins in which they are found. Leucine zippers were originally identified in several DNA-binding proteins (Landschulz et al., Science 240:1759, (1988)), and have since been found in a variety of different proteins. Among the known leucine zippers are naturally occurring peptides and derivatives thereof that dimerize or trimerize. Examples of leucine zipper domains suitable for producing soluble multimeric proteins of the invention are those described in PCT application WO 94/10308, hereby incorporated by reference. Recombinant fusion proteins comprising a polypeptide of the invention fused to a polypeptide sequence that dimerizes or trimerizes in solution are expressed in suitable host cells, and the resulting soluble multimeric fusion protein is recovered from the culture supernatant using techniques known in the art.

**[0917]** Trimeric polypeptides of the invention may offer the advantage of enhanced biological activity. Preferred leucine zipper moieties and isoleucine moieties are those that preferentially form trimers. One example is a leucine zipper derived from lung surfactant protein D (SPD), as described in Hoppe et al. (FEBS Letters 344:191, (1994)) and in U.S. patent application Ser. No. 08/446,922, hereby incorporated by reference. Other peptides derived from naturally occurring trimeric proteins may be employed in preparing trimeric polypeptides of the invention.

**[0918]** In another example, proteins of the invention are associated by interactions between Flag® polypeptide sequence contained in fusion proteins of the invention



containing Flag® polypeptide sequence. In a further embodiment, associations proteins of the invention are associated by interactions between heterologous polypeptide sequence contained in Flag® fusion proteins of the invention and anti-Flag® antibody.

[0919] The multimers of the invention may be generated using chemical techniques known in the art. For example, polypeptides desired to be contained in the multimers of the invention may be chemically cross-linked using linker molecules and linker molecule length optimization techniques known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

Additionally, multimers of the invention may be generated using techniques known in the art to form one or more inter-molecule cross-links between the cysteine residues located within the sequence of the polypeptides desired to be contained in the multimer (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Further, polypeptides of the invention may be routinely modified by the addition of cysteine or biotin to the C terminus or N-terminus of the polypeptide and techniques known in the art may be applied to generate multimers containing one or more of these modified polypeptides (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). Additionally, techniques known in the art may be applied to generate liposomes containing the polypeptide components desired to be contained in the multimer of the invention (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

[0920] Alternatively, multimers of the invention may be generated using genetic engineering techniques known in the art. In one embodiment, polypeptides contained in multimers of the invention are produced recombinantly using fusion protein technology described herein or otherwise known in the art (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In a specific embodiment, polynucleotides coding for a homodimer of the invention are generated by ligating a polynucleotide sequence encoding a polypeptide of the invention to a sequence encoding a linker polypeptide and then further to a synthetic polynucleotide encoding the translated product of the polypeptide in the reverse

orientation from the original C-terminus to the N-terminus (lacking the leader sequence) (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety). In another embodiment, recombinant techniques described herein or otherwise known in the art are applied to generate recombinant polypeptides of the invention which contain a transmembrane domain (or hydrophobic or signal peptide) and which can be incorporated by membrane reconstitution techniques into liposomes (see, e.g., US Patent Number 5,478,925, which is herein incorporated by reference in its entirety).

**[0921] Uses of the Polynucleotides**

**[0922]** Each of the polynucleotides identified herein can be used in numerous ways as reagents. The following description should be considered exemplary and utilizes known techniques.

**[0923]** The polynucleotides of the present invention are useful for chromosome identification. There exists an ongoing need to identify new chromosome markers, since few chromosome marking reagents, based on actual sequence data (repeat polymorphisms), are presently available. Each polynucleotide of the present invention can be used as a chromosome marker.

**[0924]** Briefly, sequences can be mapped to chromosomes by preparing PCR primers (preferably 15-25 bp) from the sequences shown in SEQ ID NO:X. Primers can be selected using computer analysis so that primers do not span more than one predicted exon in the genomic DNA. These primers are then used for PCR screening of somatic cell hybrids containing individual human chromosomes. Only those hybrids containing the human gene corresponding to the SEQ ID NO:X will yield an amplified fragment.

**[0925]** Similarly, somatic hybrids provide a rapid method of PCR mapping the polynucleotides to particular chromosomes. Three or more clones can be assigned per day using a single thermal cycler. Moreover, sublocalization of the polynucleotides can be achieved with panels of specific chromosome fragments. Other gene mapping strategies that can be used include in situ hybridization, prescreening with labeled

flow-sorted chromosomes, and preselection by hybridization to construct chromosome specific-cDNA libraries.

[0926] Precise chromosomal location of the polynucleotides can also be achieved using fluorescence in situ hybridization (FISH) of a metaphase chromosomal spread. This technique uses polynucleotides as short as 500 or 600 bases; however, polynucleotides 2,000-4,000 bp are preferred. For a review of this technique, see Verma et al., "Human Chromosomes: a Manual of Basic Techniques," Pergamon Press, New York (1988).

[0927] For chromosome mapping, the polynucleotides can be used individually (to mark a single chromosome or a single site on that chromosome) or in panels (for marking multiple sites and/or multiple chromosomes). Preferred polynucleotides correspond to the noncoding regions of the cDNAs because the coding sequences are more likely conserved within gene families, thus increasing the chance of cross hybridization during chromosomal mapping.

[0928] Once a polynucleotide has been mapped to a precise chromosomal location, the physical position of the polynucleotide can be used in linkage analysis. Linkage analysis establishes coinheritance between a chromosomal location and presentation of a particular disease. (Disease mapping data are found, for example, in V. McKusick, Mendelian Inheritance in Man (available on line through Johns Hopkins University Welch Medical Library) .) Assuming 1 megabase mapping resolution and one gene per 20 kb, a cDNA precisely localized to a chromosomal region associated with the disease could be one of 50-500 potential causative genes.

[0929] Thus, once coinheritance is established, differences in the polynucleotide and the corresponding gene between affected and unaffected individuals can be examined. First, visible structural alterations in the chromosomes, such as deletions or translocations, are examined in chromosome spreads or by PCR. If no structural alterations exist, the presence of point mutations are ascertained. Mutations observed in some or all affected individuals, but not in normal individuals, indicates that the mutation may cause the disease. However, complete sequencing of the polypeptide and the corresponding gene from several normal individuals is required to distinguish

the mutation from a polymorphism. If a new polymorphism is identified, this polymorphic polypeptide can be used for further linkage analysis.

**[0930]** Furthermore, increased or decreased expression of the gene in affected individuals as compared to unaffected individuals can be assessed using polynucleotides of the present invention. Any of these alterations (altered expression, chromosomal rearrangement, or mutation) can be used as a diagnostic or prognostic marker.

**[0931]** Thus, the invention also provides a diagnostic method useful during diagnosis of a disorder, involving measuring the expression level of polynucleotides of the present invention in cells or body fluid from an individual and comparing the measured gene expression level with a standard level of polynucleotide expression level, whereby an increase or decrease in the gene expression level compared to the standard is indicative of a disorder.

**[0932]** In still another embodiment, the invention includes a kit for analyzing samples for the presence of proliferative and/or cancerous polynucleotides derived from a test subject. In a general embodiment, the kit includes at least one polynucleotide probe containing a nucleotide sequence that will specifically hybridize with a polynucleotide of the present invention and a suitable container. In a specific embodiment, the kit includes two polynucleotide probes defining an internal region of the polynucleotide of the present invention, where each probe has one strand containing a 31' mer-end internal to the region. In a further embodiment, the probes may be useful as primers for polymerase chain reaction amplification.

**[0933]** Where a diagnosis of a disorder, has already been made according to conventional methods, the present invention is useful as a prognostic indicator, whereby patients exhibiting enhanced or depressed polynucleotide of the present invention expression will experience a worse clinical outcome relative to patients expressing the gene at a level nearer the standard level.

**[0934]** By "measuring the expression level of polynucleotide of the present invention" is intended qualitatively or quantitatively measuring or estimating the level of the polypeptide of the present invention or the level of the mRNA encoding the polypeptide in a first biological sample either directly (e.g., by determining or

estimating absolute protein level or mRNA level) or relatively (e.g., by comparing to the polypeptide level or mRNA level in a second biological sample). Preferably, the polypeptide level or mRNA level in the first biological sample is measured or estimated and compared to a standard polypeptide level or mRNA level, the standard being taken from a second biological sample obtained from an individual not having the disorder or being determined by averaging levels from a population of individuals not having a disorder. As will be appreciated in the art, once a standard polypeptide level or mRNA level is known, it can be used repeatedly as a standard for comparison.

**[0935]** By "biological sample" is intended any biological sample obtained from an individual, body fluid, cell line, tissue culture, or other source which contains the polypeptide of the present invention or mRNA. As indicated, biological samples include body fluids (such as semen, lymph, sera, plasma, urine, synovial fluid and spinal fluid) which contain the polypeptide of the present invention, and other tissue sources found to express the polypeptide of the present invention. Methods for obtaining tissue biopsies and body fluids from mammals are well known in the art. Where the biological sample is to include mRNA, a tissue biopsy is the preferred source.

**[0936]** The method(s) provided above may preferably be applied in a diagnostic method and/or kits in which polynucleotides and/or polypeptides are attached to a solid support. In one exemplary method, the support may be a "gene chip" or a "biological chip" as described in US Patents 5,837,832, 5,874,219, and 5,856,174. Further, such a gene chip with polynucleotides of the present invention attached may be used to identify polymorphisms between the polynucleotide sequences, with polynucleotides isolated from a test subject. The knowledge of such polymorphisms (i.e. their location, as well as, their existence) would be beneficial in identifying disease loci for many disorders, including cancerous diseases and conditions. Such a method is described in US Patents 5,858,659 and 5,856,104. The US Patents referenced supra are hereby incorporated by reference in their entirety herein.

**[0937]** The present invention encompasses polynucleotides of the present invention that are chemically synthesized, or reproduced as peptide nucleic acids (PNA), or

according to other methods known in the art. The use of PNAs would serve as the preferred form if the polynucleotides are incorporated onto a solid support, or gene chip. For the purposes of the present invention, a peptide nucleic acid (PNA) is a polyamide type of DNA analog and the monomeric units for adenine, guanine, thymine and cytosine are available commercially (Perceptive Biosystems). Certain components of DNA, such as phosphorus, phosphorus oxides, or deoxyribose derivatives, are not present in PNAs. As disclosed by P. E. Nielsen, M. Egholm, R. H. Berg and O. Buchardt, *Science* 254, 1497 (1991); and M. Egholm, O. Buchardt, L. Christensen, C. Behrens, S. M. Freier, D. A. Driver, R. H. Berg, S. K. Kim, B. Norden, and P. E. Nielsen, *Nature* 365, 666 (1993), PNAs bind specifically and tightly to complementary DNA strands and are not degraded by nucleases. In fact, PNA binds more strongly to DNA than DNA itself does. This is probably because there is no electrostatic repulsion between the two strands, and also the polyamide backbone is more flexible. Because of this, PNA/DNA duplexes bind under a wider range of stringency conditions than DNA/DNA duplexes, making it easier to perform multiplex hybridization. Smaller probes can be used than with DNA due to the strong binding. In addition, it is more likely that single base mismatches can be determined with PNA/DNA hybridization because a single mismatch in a PNA/DNA 15-mer lowers the melting point ( $T_{sub.m}$ ) by 8°-20° C, vs. 4°-16° C for the DNA/DNA 15-mer duplex. Also, the absence of charge groups in PNA means that hybridization can be done at low ionic strengths and reduce possible interference by salt during the analysis.

**[0938]** The present invention is useful for detecting cancer in mammals. In particular the invention is useful during diagnosis of pathological cell proliferative neoplasias which include, but are not limited to: acute myelogenous leukemias including acute monocytic leukemia, acute myeloblastic leukemia, acute promyelocytic leukemia, acute myelomonocytic leukemia, acute erythroleukemia, acute megakaryocytic leukemia, and acute undifferentiated leukemia, etc.; and chronic myelogenous leukemias including chronic myelomonocytic leukemia, chronic granulocytic leukemia, etc. Preferred mammals include monkeys, apes, cats, dogs, cows, pigs, horses, rabbits and humans. Particularly preferred are humans.

[0939] Pathological cell proliferative diseases, disorders, and/or conditions are often associated with inappropriate activation of proto-oncogenes. (Germann, E. P. et al., "The Etiology of Acute Leukemia: Molecular Genetics and Viral Oncology," in *Neoplastic Diseases of the Blood*, Vol 1., Wiernik, P. H. et al. eds., 161-182 (1985)). Neoplasias are now believed to result from the qualitative alteration of a normal cellular gene product, or from the quantitative modification of gene expression by insertion into the chromosome of a viral sequence, by chromosomal translocation of a gene to a more actively transcribed region, or by some other mechanism. (Germann et al., supra) It is likely that mutated or altered expression of specific genes is involved in the pathogenesis of some leukemias, among other tissues and cell types. (Germann et al., supra) Indeed, the human counterparts of the oncogenes involved in some animal neoplasias have been amplified or translocated in some cases of human leukemia and carcinoma. (Germann et al., supra)

For example, c-myc expression is highly amplified in the non-lymphocytic leukemia cell line HL-60. When HL-60 cells are chemically induced to stop proliferation, the level of c-myc is found to be downregulated. (International Publication Number WO 91/15580) However, it has been shown that exposure of HL-60 cells to a DNA construct that is complementary to the 5' end of c-myc or c-myb blocks translation of the corresponding mRNAs which downregulates expression of the c-myc or c-myb proteins and causes arrest of cell proliferation and differentiation of the treated cells. (International Publication Number WO 91/15580; Wickstrom et al., *Proc. Natl. Acad. Sci.* 85:1028 (1988); Anfossi et al., *Proc. Natl. Acad. Sci.* 86:3379 (1989)). However, the skilled artisan would appreciate the present invention's usefulness would not be limited to treatment of proliferative diseases, disorders, and/or conditions of hematopoietic cells and tissues, in light of the numerous cells and cell types of varying origins which are known to exhibit proliferative phenotypes.

[0940] In addition to the foregoing, a polynucleotide can be used to control gene expression through triple helix formation or antisense DNA or RNA. Antisense techniques are discussed, for example, in Okano, J. *Neurochem.* 56: 560 (1991); "Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance Lee et al.,

Nucleic Acids Research 6: 3073 (1979); Cooney et al., Science 241: 456 (1988); and Dervan et al., Science 251: 1360 (1991). Both methods rely on binding of the polynucleotide to a complementary DNA or RNA. For these techniques, preferred polynucleotides are usually oligonucleotides 20 to 40 bases in length and complementary to either the region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res. 6:3073 (1979); Cooney et al., Science 241:456 (1988); and Dervan et al., Science 251:1360 (1991) ) or to the mRNA itself (antisense - Okano, J. Neurochem. 56:560 (1991); Oligodeoxy-nucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).) Triple helix formation optimally results in a shut-off of RNA transcription from DNA, while antisense RNA hybridization blocks translation of an mRNA molecule into polypeptide. Both techniques are effective in model systems, and the information disclosed herein can be used to design antisense or triple helix polynucleotides in an effort to treat or prevent disease.

[0941] Polynucleotides of the present invention are also useful in gene therapy. One goal of gene therapy is to insert a normal gene into an organism having a defective gene, in an effort to correct the genetic defect. The polynucleotides disclosed in the present invention offer a means of targeting such genetic defects in a highly accurate manner. Another goal is to insert a new gene that was not present in the host genome, thereby producing a new trait in the host cell.

[0942] The polynucleotides are also useful for identifying individuals from minute biological samples. The United States military, for example, is considering the use of restriction fragment length polymorphism (RFLP) for identification of its personnel. In this technique, an individual's genomic DNA is digested with one or more restriction enzymes, and probed on a Southern blot to yield unique bands for identifying personnel. This method does not suffer from the current limitations of "Dog Tags" which can be lost, switched, or stolen, making positive identification difficult. The polynucleotides of the present invention can be used as additional DNA markers for RFLP.

[0943] The polynucleotides of the present invention can also be used as an alternative to RFLP, by determining the actual base-by-base DNA sequence of selected portions



of an individual's genome. These sequences can be used to prepare PCR primers for amplifying and isolating such selected DNA, which can then be sequenced. Using this technique, individuals can be identified because each individual will have a unique set of DNA sequences. Once an unique ID database is established for an individual, positive identification of that individual, living or dead, can be made from extremely small tissue samples.

[0944] Forensic biology also benefits from using DNA-based identification techniques as disclosed herein. DNA sequences taken from very small biological samples such as tissues, e.g., hair or skin, or body fluids, e.g., blood, saliva, semen, synovial fluid, amniotic fluid, breast milk, lymph, pulmonary sputum or surfactant, urine, fecal matter, etc., can be amplified using PCR. In one prior art technique, gene sequences amplified from polymorphic loci, such as DQa class II HLA gene, are used in forensic biology to identify individuals. (Erlich, H., PCR Technology, Freeman and Co. (1992).) Once these specific polymorphic loci are amplified, they are digested with one or more restriction enzymes, yielding an identifying set of bands on a Southern blot probed with DNA corresponding to the DQa class II HLA gene. Similarly, polynucleotides of the present invention can be used as polymorphic markers for forensic purposes.

[0945] There is also a need for reagents capable of identifying the source of a particular tissue. Such need arises, for example, in forensics when presented with tissue of unknown origin. Appropriate reagents can comprise, for example, DNA probes or primers specific to particular tissue prepared from the sequences of the present invention. Panels of such reagents can identify tissue by species and/or by organ type. In a similar fashion, these reagents can be used to screen tissue cultures for contamination.

[0946] In the very least, the polynucleotides of the present invention can be used as molecular weight markers on Southern gels, as diagnostic probes for the presence of a specific mRNA in a particular cell type, as a probe to "subtract-out" known sequences in the process of discovering novel polynucleotides, for selecting and making oligomers for attachment to a "gene chip" or other support, to raise anti-DNA

antibodies using DNA immunization techniques, and as an antigen to elicit an immune response.

**[0947] Uses of the Polypeptides**

**[0948]** Each of the polypeptides identified herein can be used in numerous ways. The following description should be considered exemplary and utilizes known techniques.

**[0949]** A polypeptide of the present invention can be used to assay protein levels in a biological sample using antibody-based techniques. For example, protein expression in tissues can be studied with classical immunohistological methods. (Jalkanen, M., et al., J. Cell. Biol. 101:976-985 (1985); Jalkanen, M., et al., J. Cell . Biol. 105:3087-3096 (1987).) Other antibody-based methods useful for detecting protein gene expression include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA). Suitable antibody assay labels are known in the art and include enzyme labels, such as, glucose oxidase, and radioisotopes, such as iodine ( $^{125}\text{I}$ ,  $^{121}\text{I}$ ), carbon ( $^{14}\text{C}$ ), sulfur ( $^{35}\text{S}$ ), tritium ( $^3\text{H}$ ), indium ( $^{112}\text{In}$ ), and technetium ( $^{99\text{m}}\text{Tc}$ ), and fluorescent labels, such as fluorescein and rhodamine, and biotin.

**[0950]** In addition to assaying secreted protein levels in a biological sample, proteins can also be detected in vivo by imaging. Antibody labels or markers for in vivo imaging of protein include those detectable by X-radiography, NMR or ESR. For X-radiography, suitable labels include radioisotopes such as barium or cesium, which emit detectable radiation but are not overtly harmful to the subject. Suitable markers for NMR and ESR include those with a detectable characteristic spin, such as deuterium, which may be incorporated into the antibody by labeling of nutrients for the relevant hybridoma.

**[0951]** A protein-specific antibody or antibody fragment which has been labeled with an appropriate detectable imaging moiety, such as a radioisotope (for example,  $^{131}\text{I}$ ,  $^{112}\text{In}$ ,  $^{99\text{m}}\text{Tc}$ ), a radio-opaque substance, or a material detectable by nuclear magnetic resonance, is introduced (for example, parenterally, subcutaneously, or intraperitoneally) into the mammal. It will be understood in the art that the size of the subject and the imaging system used will determine the quantity of imaging moiety

needed to produce diagnostic images. In the case of a radioisotope moiety, for a human subject, the quantity of radioactivity injected will normally range from about 5 to 20 millicuries of  $^{99m}\text{Tc}$ . The labeled antibody or antibody fragment will then preferentially accumulate at the location of cells which contain the specific protein. In vivo tumor imaging is described in S.W. Burchiel et al., "Immunopharmacokinetics of Radiolabeled Antibodies and Their Fragments." (Chapter 13 in Tumor Imaging: The Radiochemical Detection of Cancer, S.W. Burchiel and B. A. Rhodes, eds., Masson Publishing Inc. (1982).)

[0952] Thus, the invention provides a diagnostic method of a disorder, which involves (a) assaying the expression of a polypeptide of the present invention in cells or body fluid of an individual; (b) comparing the level of gene expression with a standard gene expression level, whereby an increase or decrease in the assayed polypeptide gene expression level compared to the standard expression level is indicative of a disorder. With respect to cancer, the presence of a relatively high amount of transcript in biopsied tissue from an individual may indicate a predisposition for the development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

[0953] Moreover, polypeptides of the present invention can be used to treat, prevent, and/or diagnose disease. For example, patients can be administered a polypeptide of the present invention in an effort to replace absent or decreased levels of the polypeptide (e.g., insulin), to supplement absent or decreased levels of a different polypeptide (e.g., hemoglobin S for hemoglobin B, SOD, catalase, DNA repair proteins), to inhibit the activity of a polypeptide (e.g., an oncogene or tumor suppressor), to activate the activity of a polypeptide (e.g., by binding to a receptor), to reduce the activity of a membrane bound receptor by competing with it for free ligand (e.g., soluble TNF receptors used in reducing inflammation), or to bring about a desired response (e.g., blood vessel growth inhibition, enhancement of the immune response to proliferative cells or tissues).

**[0954]** Similarly, antibodies directed to a polypeptide of the present invention can also be used to treat, prevent, and/or diagnose disease. For example, administration of an antibody directed to a polypeptide of the present invention can bind and reduce overproduction of the polypeptide. Similarly, administration of an antibody can activate the polypeptide, such as by binding to a polypeptide bound to a membrane (receptor).

**[0955]** At the very least, the polypeptides of the present invention can be used as molecular weight markers on SDS-PAGE gels or on molecular sieve gel filtration columns using methods well known to those of skill in the art. Polypeptides can also be used to raise antibodies, which in turn are used to measure protein expression from a recombinant cell, as a way of assessing transformation of the host cell. Moreover, the polypeptides of the present invention can be used to test the following biological activities.

**[0956] Gene Therapy Methods**

**[0957]** Another aspect of the present invention is to gene therapy methods for treating or preventing disorders, diseases and conditions. The gene therapy methods relate to the introduction of nucleic acid (DNA, RNA and antisense DNA or RNA) sequences into an animal to achieve expression of a polypeptide of the present invention. This method requires a polynucleotide which codes for a polypeptide of the invention that operatively linked to a promoter and any other genetic elements necessary for the expression of the polypeptide by the target tissue. Such gene therapy and delivery techniques are known in the art, see, for example, WO90/11092, which is herein incorporated by reference.

**[0958]** Thus, for example, cells from a patient may be engineered with a polynucleotide (DNA or RNA) comprising a promoter operably linked to a polynucleotide of the invention *ex vivo*, with the engineered cells then being provided to a patient to be treated with the polypeptide. Such methods are well-known in the art. For example, see Belldgrun et al., J. Natl. Cancer Inst., 85:207-216 (1993); Ferrantini et al., Cancer Research, 53:107-1112 (1993); Ferrantini et al., J. Immunology 153: 4604-4615 (1994); Kaido, T., et al., Int. J. Cancer 60: 221-229 (1995); Ogura et al., Cancer Research 50: 5102-5106 (1990); Santodonato, et al., Human Gene Therapy 7:1-10 (1996); Santodonato, et al., Gene Therapy 4:1246-1255 (1997); and Zhang, et al., Cancer Gene Therapy 3: 31-38 (1996)), which are herein incorporated by reference. In one embodiment, the cells which are engineered are arterial cells. The arterial cells may be reintroduced into the patient through direct injection to the artery, the tissues surrounding the artery, or through catheter injection.

**[0959]** As discussed in more detail below, the polynucleotide constructs can be delivered by any method that delivers injectable materials to the cells of an animal, such as, injection into the interstitial space of tissues (heart, muscle, skin, lung, liver, and the like). The polynucleotide constructs may be delivered in a pharmaceutically acceptable liquid or aqueous carrier.

**[0960]** In one embodiment, the polynucleotide of the invention is delivered as a naked polynucleotide. The term "naked" polynucleotide, DNA or RNA refers to sequences that are free from any delivery vehicle that acts to assist, promote or facilitate entry into the cell, including viral sequences, viral particles, liposome formulations, lipofectin or precipitating agents and the like. However, the polynucleotides of the invention can also be delivered in liposome formulations and lipofectin formulations and the like can be prepared by methods well known to those skilled in the art. Such methods are described, for example, in U.S. Patent Nos. 5,593,972, 5,589,466, and 5,580,859, which are herein incorporated by reference.

**[0961]** The polynucleotide vector constructs of the invention used in the gene therapy method are preferably constructs that will not integrate into the host genome nor will they contain sequences that allow for replication. Appropriate vectors include pWLNEO, pSV2CAT, pOG44, pXT1 and pSG available from Stratagene; pSVK3, pBPV, pMSG and pSVL available from Pharmacia; and pEF1/V5, pcDNA3.1, and pRc/CMV2 available from Invitrogen. Other suitable vectors will be readily apparent to the skilled artisan.

**[0962]** Any strong promoter known to those skilled in the art can be used for driving the expression of polynucleotide sequence of the invention. Suitable promoters include adenoviral promoters, such as the adenoviral major late promoter; or heterologous promoters, such as the cytomegalovirus (CMV) promoter; the respiratory syncytial virus (RSV) promoter; inducible promoters, such as the MMT promoter, the metallothionein promoter; heat shock promoters; the albumin promoter; the ApoAI promoter; human globin promoters; viral thymidine kinase promoters, such as the Herpes Simplex thymidine kinase promoter; retroviral LTRs; the b-actin promoter; and human growth hormone promoters. The promoter also may be the native promoter for the polynucleotides of the invention.

**[0963]** Unlike other gene therapy techniques, one major advantage of introducing naked nucleic acid sequences into target cells is the transitory nature of the polynucleotide synthesis in the cells. Studies have shown that non-replicating DNA sequences can be introduced into cells to provide production of the desired polypeptide for periods of up to six months.

[0964] The polynucleotide construct of the invention can be delivered to the interstitial space of tissues within the an animal, including of muscle, skin, brain, lung, liver, spleen, bone marrow, thymus, heart, lymph, blood, bone, cartilage, pancreas, kidney, gall bladder, stomach, intestine, testis, ovary, uterus, rectum, nervous system, eye, gland, and connective tissue. Interstitial space of the tissues comprises the intercellular, fluid, mucopolysaccharide matrix among the reticular fibers of organ tissues, elastic fibers in the walls of vessels or chambers, collagen fibers of fibrous tissues, or that same matrix within connective tissue ensheathing muscle cells or in the lacunae of bone. It is similarly the space occupied by the plasma of the circulation and the lymph fluid of the lymphatic channels. Delivery to the interstitial space of muscle tissue is preferred for the reasons discussed below. They may be conveniently delivered by injection into the tissues comprising these cells. They are preferably delivered to and expressed in persistent, non-dividing cells which are differentiated, although delivery and expression may be achieved in non-differentiated or less completely differentiated cells, such as, for example, stem cells of blood or skin fibroblasts. *In vivo* muscle cells are particularly competent in their ability to take up and express polynucleotides.

[0965] For the naked *nucleic acid* sequence injection, an effective dosage amount of DNA or RNA will be in the range of from about 0.05 mg/kg body weight to about 50 mg/kg body weight. Preferably the dosage will be from about 0.005 mg/kg to about 20 mg/kg and more preferably from about 0.05 mg/kg to about 5 mg/kg. Of course, as the artisan of ordinary skill will appreciate, this dosage will vary according to the tissue site of injection. The appropriate and effective dosage of nucleic acid sequence can readily be determined by those of ordinary skill in the art and may depend on the condition being treated and the route of administration.

[0966] The preferred route of administration is by the parenteral route of injection into the interstitial space of tissues. However, other parenteral routes may also be used, such as, inhalation of an aerosol formulation particularly for delivery to lungs or bronchial tissues, throat or mucous membranes of the nose. In addition, naked DNA constructs can be delivered to arteries during angioplasty by the catheter used in the procedure.

**[0967]** The naked polynucleotides are delivered by any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, and so-called "gene guns". These delivery methods are known in the art.

**[0968]** The constructs may also be delivered with delivery vehicles such as viral sequences, viral particles, liposome formulations, lipofectin, precipitating agents, etc. Such methods of delivery are known in the art.

**[0969]** In certain embodiments, the polynucleotide constructs of the invention are complexed in a liposome preparation. Liposomal preparations for use in the instant invention include cationic (positively charged), anionic (negatively charged) and neutral preparations. However, cationic liposomes are particularly preferred because a tight charge complex can be formed between the cationic liposome and the polyanionic nucleic acid. Cationic liposomes have been shown to mediate intracellular delivery of plasmid DNA (Felgner et al., Proc. Natl. Acad. Sci. USA , 84:7413-7416 (1987), which is herein incorporated by reference); mRNA (Malone et al., Proc. Natl. Acad. Sci. USA , 86:6077-6081 (1989), which is herein incorporated by reference); and purified transcription factors (Debs et al., J. Biol. Chem., 265:10189-10192 (1990), which is herein incorporated by reference), in functional form.

**[0970]** Cationic liposomes are readily available. For example, N[1-2,3-dioleoyloxy)propyl]-N,N,N-triethylammonium (DOTMA) liposomes are particularly useful and are available under the trademark Lipofectin, from GIBCO BRL, Grand Island, N.Y. (See, also, Felgner et al., Proc. Natl Acad. Sci. USA , 84:7413-7416 (1987), which is herein incorporated by reference). Other commercially available liposomes include transfectace (DDAB/DOPE) and DOTAP/DOPE (Boehringer).



[0971] Other cationic liposomes can be prepared from readily available materials using techniques well known in the art. See, e.g. PCT Publication NO: WO 90/11092 (which is herein incorporated by reference) for a description of the synthesis of DOTAP (1,2-bis(oleoyloxy)-3-(trimethylammonio)propane) liposomes. Preparation of DOTMA liposomes is explained in the literature, see, e.g., Felgner et al., Proc. Natl. Acad. Sci. USA, 84:7413-7417, which is herein incorporated by reference. Similar methods can be used to prepare liposomes from other cationic lipid materials.

[0972] Similarly, anionic and neutral liposomes are readily available, such as from Avanti Polar Lipids (Birmingham, Ala.), or can be easily prepared using readily available materials. Such materials include phosphatidyl, choline, cholesterol, phosphatidyl ethanolamine, dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), dioleoylphosphatidyl ethanolamine (DOPE), among others. These materials can also be mixed with the DOTMA and DOTAP starting materials in appropriate ratios. Methods for making liposomes using these materials are well known in the art.

[0973] For example, commercially dioleoylphosphatidyl choline (DOPC), dioleoylphosphatidyl glycerol (DOPG), and dioleoylphosphatidyl ethanolamine (DOPE) can be used in various combinations to make conventional liposomes, with or without the addition of cholesterol. Thus, for example, DOPG/DOPC vesicles can be prepared by drying 50 mg each of DOPG and DOPC under a stream of nitrogen gas into a sonication vial. The sample is placed under a vacuum pump overnight and is hydrated the following day with deionized water. The sample is then sonicated for 2 hours in a capped vial, using a Heat Systems model 350 sonicator equipped with an inverted cup (bath type) probe at the maximum setting while the bath is circulated at 15EC. Alternatively, negatively charged vesicles can be prepared without sonication to produce multilamellar vesicles or by extrusion through nucleopore membranes to produce unilamellar vesicles of discrete size. Other methods are known and available to those of skill in the art.

[0974] The liposomes can comprise multilamellar vesicles (MLVs), small unilamellar vesicles (SUVs), or large unilamellar vesicles (LUVs), with SUVs being preferred. The various liposome-nucleic acid complexes are prepared using methods well known in the art. See, e.g., Straubinger et al., *Methods of Immunology*, 101:512-527 (1983), which is herein incorporated by reference. For example, MLVs containing nucleic acid can be prepared by depositing a thin film of phospholipid on the walls of a glass tube and subsequently hydrating with a solution of the material to be encapsulated. SUVs are prepared by extended sonication of MLVs to produce a homogeneous population of unilamellar liposomes. The material to be entrapped is added to a suspension of preformed MLVs and then sonicated. When using liposomes containing cationic lipids, the dried lipid film is resuspended in an appropriate solution such as sterile water or an isotonic buffer solution such as 10 mM Tris/NaCl, sonicated, and then the preformed liposomes are mixed directly with the DNA. The liposome and DNA form a very stable complex due to binding of the positively charged liposomes to the cationic DNA. SUVs find use with small nucleic acid fragments. LUVs are prepared by a number of methods, well known in the art. Commonly used methods include  $\text{Ca}^{2+}$ -EDTA chelation (Papahadjopoulos et al., *Biochim. Biophys. Acta*, 394:483 (1975); Wilson et al., *Cell*, 17:77 (1979)); ether injection (Deamer et al., *Biochim. Biophys. Acta*, 443:629 (1976); Ostro et al., *Biochem. Biophys. Res. Commun.*, 76:836 (1977); Fraley et al., *Proc. Natl. Acad. Sci. USA*, 76:3348 (1979)); detergent dialysis (Enoch et al., *Proc. Natl. Acad. Sci. USA*, 76:145 (1979)); and reverse-phase evaporation (REV) (Fraley et al., *J. Biol. Chem.*, 255:10431 (1980); Szoka et al., *Proc. Natl. Acad. Sci. USA*, 75:145 (1978); Schaefer-Ridder et al., *Science*, 215:166 (1982)), which are herein incorporated by reference.

[0975] Generally, the ratio of DNA to liposomes will be from about 10:1 to about 1:10. Preferably, the ration will be from about 5:1 to about 1:5. More preferably, the ration will be about 3:1 to about 1:3. Still more preferably, the ratio will be about 1:1.

[0976] U.S. Patent NO: 5,676,954 (which is herein incorporated by reference) reports on the injection of genetic material, complexed with cationic liposomes carriers, into mice. U.S. Patent Nos. 4,897,355, 4,946,787, 5,049,386, 5,459,127, 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication NO: WO 94/9469 (which are herein incorporated by reference) provide cationic lipids for use in transfecting DNA into cells and mammals. U.S. Patent Nos. 5,589,466, 5,693,622, 5,580,859, 5,703,055, and international publication NO: WO 94/9469 (which are herein incorporated by reference) provide methods for delivering DNA-cationic lipid complexes to mammals.

[0977] In certain embodiments, cells are engineered, *ex vivo* or *in vivo*, using a retroviral particle containing RNA which comprises a sequence encoding polypeptides of the invention. Retroviruses from which the retroviral plasmid vectors may be derived include, but are not limited to, Moloney Murine Leukemia Virus, spleen necrosis virus, Rous sarcoma Virus, Harvey Sarcoma Virus, avian leukosis virus, gibbon ape leukemia virus, human immunodeficiency virus, Myeloproliferative Sarcoma Virus, and mammary tumor virus.

[0978] The retroviral plasmid vector is employed to transduce packaging cell lines to form producer cell lines. Examples of packaging cells which may be transfected include, but are not limited to, the PE501, PA317, R-2, R-AM, PA12, T19-14X, VT-19-17-H2, RCRE, RCRIP, GP+E-86, GP+envAm12, and DAN cell lines as described in Miller, Human Gene Therapy, 1:5-14 (1990), which is incorporated herein by reference in its entirety. The vector may transduce the packaging cells through any means known in the art. Such means include, but are not limited to, electroporation, the use of liposomes, and CaPO<sub>4</sub> precipitation. In one alternative, the retroviral plasmid vector may be encapsulated into a liposome, or coupled to a lipid, and then administered to a host.

[0979] The producer cell line generates infectious retroviral vector particles which include polynucleotide encoding polypeptides of the invention. Such retroviral vector particles then may be employed, to transduce eukaryotic cells, either *in vitro* or *in vivo*. The transduced eukaryotic cells will express polypeptides of the invention.

**[0980]** In certain other embodiments, cells are engineered, *ex vivo* or *in vivo*, with polynucleotides of the invention contained in an adenovirus vector. Adenovirus can be manipulated such that it encodes and expresses polypeptides of the invention, and at the same time is inactivated in terms of its ability to replicate in a normal lytic viral life cycle. Adenovirus expression is achieved without integration of the viral DNA into the host cell chromosome, thereby alleviating concerns about insertional mutagenesis. Furthermore, adenoviruses have been used as live enteric vaccines for many years with an excellent safety profile (Schwartz et al., Am. Rev. Respir. Dis., 109:233-238 (1974)). Finally, adenovirus mediated gene transfer has been demonstrated in a number of instances including transfer of alpha-1-antitrypsin and CFTR to the lungs of cotton rats (Rosenfeld et al., Science, 252:431-434 (1991); Rosenfeld et al., Cell, 68:143-155 (1992)). Furthermore, extensive studies to attempt to establish adenovirus as a causative agent in human cancer were uniformly negative (Green et al. Proc. Natl. Acad. Sci. USA, 76:6606 (1979)).

**[0981]** Suitable adenoviral vectors useful in the present invention are described, for example, in Kozarsky and Wilson, Curr. Opin. Genet. Devel., 3:499-503 (1993); Rosenfeld et al., Cell, 68:143-155 (1992); Engelhardt et al., Human Genet. Ther., 4:759-769 (1993); Yang et al., Nature Genet., 7:362-369 (1994); Wilson et al., Nature, 365:691-692 (1993); and U.S. Patent NO: 5,652,224, which are herein incorporated by reference. For example, the adenovirus vector Ad2 is useful and can be grown in human 293 cells. These cells contain the E1 region of adenovirus and constitutively express Ela and Elb, which complement the defective adenoviruses by providing the products of the genes deleted from the vector. In addition to Ad2, other varieties of adenovirus (e.g., Ad3, Ad5, and Ad7) are also useful in the present invention.

[0982] Preferably, the adenoviruses used in the present invention are replication deficient. Replication deficient adenoviruses require the aid of a helper virus and/or packaging cell line to form infectious particles. The resulting virus is capable of infecting cells and can express a polynucleotide of interest which is operably linked to a promoter, but cannot replicate in most cells. Replication deficient adenoviruses may be deleted in one or more of all or a portion of the following genes: E1a, E1b, E3, E4, E2a, or L1 through L5.

[0983] In certain other embodiments, the cells are engineered, *ex vivo* or *in vivo*, using an adeno-associated virus (AAV). AAVs are naturally occurring defective viruses that require helper viruses to produce infectious particles (Muzyczka, Curr. Topics in Microbiol. Immunol., 158:97 (1992)). It is also one of the few viruses that may integrate its DNA into non-dividing cells. Vectors containing as little as 300 base pairs of AAV can be packaged and can integrate, but space for exogenous DNA is limited to about 4.5 kb. Methods for producing and using such AAVs are known in the art. See, for example, U.S. Patent Nos. 5,139,941, 5,173,414, 5,354,678, 5,436,146, 5,474,935, 5,478,745, and 5,589,377.

[0984] For example, an appropriate AAV vector for use in the present invention will include all the sequences necessary for DNA replication, encapsidation, and host-cell integration. The polynucleotide construct containing polynucleotides of the invention is inserted into the AAV vector using standard cloning methods, such as those found in Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Press (1989). The recombinant AAV vector is then transfected into packaging cells which are infected with a helper virus, using any standard technique, including lipofection, electroporation, calcium phosphate precipitation, etc. Appropriate helper viruses include adenoviruses, cytomegaloviruses, vaccinia viruses, or herpes viruses. Once the packaging cells are transfected and infected, they will produce infectious AAV viral particles which contain the polynucleotide construct of the invention. These viral particles are then used to transduce eukaryotic cells, either *ex vivo* or *in vivo*. The transduced cells will contain the polynucleotide construct integrated into its genome, and will express the desired gene product.

**[0985]** Another method of gene therapy involves operably associating heterologous control regions and endogenous polynucleotide sequences (e.g. encoding the polypeptide sequence of interest) via homologous recombination (see, e.g., U.S. Patent NO: 5,641,670, issued June 24, 1997; International Publication NO: WO 96/29411, published September 26, 1996; International Publication NO: WO 94/12650, published August 4, 1994; Koller et al., Proc. Natl. Acad. Sci. USA, 86:8932-8935 (1989); and Zijlstra et al., Nature, 342:435-438 (1989). This method involves the activation of a gene which is present in the target cells, but which is not normally expressed in the cells, or is expressed at a lower level than desired.

**[0986]** Polynucleotide constructs are made, using standard techniques known in the art, which contain the promoter with targeting sequences flanking the promoter. Suitable promoters are described herein. The targeting sequence is sufficiently complementary to an endogenous sequence to permit homologous recombination of the promoter-targeting sequence with the endogenous sequence. The targeting sequence will be sufficiently near the 5' end of the desired endogenous polynucleotide sequence so the promoter will be operably linked to the endogenous sequence upon homologous recombination.

**[0987]** The promoter and the targeting sequences can be amplified using PCR. Preferably, the amplified promoter contains distinct restriction enzyme sites on the 5' and 3' ends. Preferably, the 3' end of the first targeting sequence contains the same restriction enzyme site as the 5' end of the amplified promoter and the 5' end of the second targeting sequence contains the same restriction site as the 3' end of the amplified promoter. The amplified promoter and targeting sequences are digested and ligated together.

**[0988]** The promoter-targeting sequence construct is delivered to the cells, either as naked polynucleotide, or in conjunction with transfection-facilitating agents, such as liposomes, viral sequences, viral particles, whole viruses, lipofection, precipitating agents, etc., described in more detail above. The P promoter-targeting sequence can be delivered by any method, included direct needle injection, intravenous injection, topical administration, catheter infusion, particle accelerators, etc. The methods are described in more detail below.

[0989] The promoter-targeting sequence construct is taken up by cells. Homologous recombination between the construct and the endogenous sequence takes place, such that an endogenous sequence is placed under the control of the promoter. The promoter then drives the expression of the endogenous sequence.

[0990] The polynucleotides encoding polypeptides of the present invention may be administered along with other polynucleotides encoding other angiogenic proteins. Angiogenic proteins include, but are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2 (VEGF-C), VEGF-3 (VEGF-B), epidermal growth factor alpha and beta, platelet-derived endothelial cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and nitric oxide synthase.

[0991] Preferably, the polynucleotide encoding a polypeptide of the invention contains a secretory signal sequence that facilitates secretion of the protein. Typically, the signal sequence is positioned in the coding region of the polynucleotide to be expressed towards or at the 5' end of the coding region. The signal sequence may be homologous or heterologous to the polynucleotide of interest and may be homologous or heterologous to the cells to be transfected. Additionally, the signal sequence may be chemically synthesized using methods known in the art.

[0992] Any mode of administration of any of the above-described polynucleotides constructs can be used so long as the mode results in the expression of one or more molecules in an amount sufficient to provide a therapeutic effect. This includes direct needle injection, systemic injection, catheter infusion, biolistic injectors, particle accelerators (i.e., "gene guns"), gelfoam sponge depots, other commercially available depot materials, osmotic pumps (e.g., Alza minipumps), oral or suppositorial solid (tablet or pill) pharmaceutical formulations, and decanting or topical applications during surgery. For example, direct injection of naked calcium phosphate-precipitated plasmid into rat liver and rat spleen or a protein-coated plasmid into the portal vein has resulted in gene expression of the foreign gene in the rat livers. (Kaneda et al., Science, 243:375 (1989)).

[0993] A preferred method of local administration is by direct injection. Preferably, a recombinant molecule of the present invention complexed with a delivery vehicle is administered by direct injection into or locally within the area of arteries.

Administration of a composition locally within the area of arteries refers to injecting the composition centimeters and preferably, millimeters within arteries.

[0994] Another method of local administration is to contact a polynucleotide construct of the present invention in or around a surgical wound. For example, a patient can undergo surgery and the polynucleotide construct can be coated on the surface of tissue inside the wound or the construct can be injected into areas of tissue inside the wound.

[0995] Therapeutic compositions useful in systemic administration, include recombinant molecules of the present invention complexed to a targeted delivery vehicle of the present invention. Suitable delivery vehicles for use with systemic administration comprise liposomes comprising ligands for targeting the vehicle to a particular site.

[0996] Preferred methods of systemic administration, include intravenous injection, aerosol, oral and percutaneous (topical) delivery. Intravenous injections can be performed using methods standard in the art. Aerosol delivery can also be performed using methods standard in the art (see, for example, Stribling et al., Proc. Natl. Acad. Sci. USA , 189:11277-11281 (1992), which is incorporated herein by reference). Oral delivery can be performed by complexing a polynucleotide construct of the present invention to a carrier capable of withstanding degradation by digestive enzymes in the gut of an animal. Examples of such carriers, include plastic capsules or tablets, such as those known in the art. Topical delivery can be performed by mixing a polynucleotide construct of the present invention with a lipophilic reagent (e.g., DMSO) that is capable of passing into the skin.



[0997] Determining an effective amount of substance to be delivered can depend upon a number of factors including, for example, the chemical structure and biological activity of the substance, the age and weight of the animal, the precise condition requiring treatment and its severity, and the route of administration. The frequency of treatments depends upon a number of factors, such as the amount of polynucleotide constructs administered per dose, as well as the health and history of the subject. The precise amount, number of doses, and timing of doses will be determined by the attending physician or veterinarian. Therapeutic compositions of the present invention can be administered to any animal, preferably to mammals and birds. Preferred mammals include humans, dogs, cats, mice, rats, rabbits sheep, cattle, horses and pigs, with humans being particularly

**[0998] Biological Activities**

[0999] The polynucleotides or polypeptides, or agonists or antagonists of the present invention can be used in assays to test for one or more biological activities. If these polynucleotides and polypeptides do exhibit activity in a particular assay, it is likely that these molecules may be involved in the diseases associated with the biological activity. Thus, the polynucleotides or polypeptides, or agonists or antagonists could be used to treat the associated disease.

**[1000] Immune Activity**

[1001] Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing diseases, disorders, and/or conditions of the immune system, by, for example, activating or inhibiting the proliferation, differentiation, or mobilization (chemotaxis) of immune cells. Immune cells develop through a process called hematopoiesis, producing myeloid (platelets, red blood cells, neutrophils, and macrophages) and lymphoid (B and T lymphocytes) cells from pluripotent stem cells. The etiology of these immune diseases, disorders, and/or conditions may be genetic, somatic, such as cancer and some autoimmune diseases, acquired (e.g., by chemotherapy or toxins), or infectious. Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of

the present invention can be used as a marker or detector of a particular immune system disease or disorder.

**[1002]** Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing diseases, disorders, and/or conditions of hematopoietic cells. Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used to increase differentiation and proliferation of hematopoietic cells, including the pluripotent stem cells, in an effort to treat or prevent those diseases, disorders, and/or conditions associated with a decrease in certain (or many) types hematopoietic cells. Examples of immunologic deficiency syndromes include, but are not limited to: blood protein diseases, disorders, and/or conditions (e.g., agammaglobulinemia, dysgammaglobulinemia), ataxia telangiectasia, common variable immunodeficiency, Digeorge Syndrome, HIV infection, HTLV-BLV infection, leukocyte adhesion deficiency syndrome, lymphopenia, phagocyte bactericidal dysfunction, severe combined immunodeficiency (SCIDs), Wiskott-Aldrich Disorder, anemia, thrombocytopenia, or hemoglobinuria.

**[1003]** Moreover, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (clot formation). For example, by increasing hemostatic or thrombolytic activity, polynucleotides or polypeptides, and/or agonists or antagonists of the present invention could be used to treat or prevent blood coagulation diseases, disorders, and/or conditions (e.g., afibrinogenemia, factor deficiencies), blood platelet diseases, disorders, and/or conditions (e.g., thrombocytopenia), or wounds resulting from trauma, surgery, or other causes. Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention that can decrease hemostatic or thrombolytic activity could be used to inhibit or dissolve clotting. These molecules could be important in the treatment or prevention of heart attacks (infarction), strokes, or scarring.

**[1004]** The polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be useful in treating, preventing, and/or diagnosing

autoimmune disorders. Many autoimmune disorders result from inappropriate recognition of self as foreign material by immune cells. This inappropriate recognition results in an immune response leading to the destruction of the host tissue. Therefore, the administration of polynucleotides and polypeptides of the invention that can inhibit an immune response, particularly the proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing autoimmune disorders.

[1005] Autoimmune diseases or disorders that may be treated, prevented, and/or diagnosed by polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention include, but are not limited to, one or more of the following: autoimmune hemolytic anemia, autoimmune neonatal thrombocytopenia, idiopathic thrombocytopenia purpura, autoimmunocytopenia, hemolytic anemia, antiphospholipid syndrome, dermatitis, allergic encephalomyelitis, myocarditis, relapsing polychondritis, rheumatic heart disease, glomerulonephritis (e.g. IgA nephropathy), Multiple Sclerosis, Neuritis, Uveitis Ophthalmia, Polyendocrinopathies, Purpura (e.g., Henloch-Scoenlein purpura), Reiter's Disease, Stiff-Man Syndrome, Autoimmune Pulmonary Inflammation, Autism, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye, autoimmune thyroiditis, hypothyroidism (i.e., Hashimoto's thyroiditis, systemic lupus erythematosus, Goodpasture's syndrome, Pemphigus, Receptor autoimmunities such as, for example, (a) Graves' Disease, (b) Myasthenia Gravis, and (c) insulin resistance, autoimmune hemolytic anemia, autoimmune thrombocytopenic purpura, rheumatoid arthritis, scleroderma with anti-collagen antibodies, mixed connective tissue disease, polymyositis/dermatomyositis, pernicious anemia, idiopathic Addison's disease, infertility, glomerulonephritis such as primary glomerulonephritis and IgA nephropathy, bullous pemphigoid, Sjogren's syndrome, diabetes mellitus, and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis), chronic active hepatitis, primary biliary cirrhosis, other endocrine gland failure, vitiligo, vasculitis, post-MI, cardiomyopathy syndrome, urticaria, atopic dermatitis, asthma, inflammatory myopathies, and other inflammatory, granulomatous, degenerative, and atrophic disorders.

[1006] Additional autoimmune disorders (that are probable) that may be treated, prevented, and/or diagnosed with the compositions of the invention include, but are not limited to, rheumatoid arthritis (often characterized, e.g., by immune complexes in joints), scleroderma with anti-collagen antibodies (often characterized, e.g., by nucleolar and other nuclear antibodies), mixed connective tissue disease (often characterized, e.g., by antibodies to extractable nuclear antigens (e.g., ribonucleoprotein)), polymyositis (often characterized, e.g., by nonhistone ANA), pernicious anemia (often characterized, e.g., by antiparietal cell, microsomes, and intrinsic factor antibodies), idiopathic Addison's disease (often characterized, e.g., by humoral and cell-mediated adrenal cytotoxicity, infertility (often characterized, e.g., by antispermatozoal antibodies), glomerulonephritis (often characterized, e.g., by glomerular basement membrane antibodies or immune complexes), bullous pemphigoid (often characterized, e.g., by IgG and complement in basement membrane), Sjogren's syndrome (often characterized, e.g., by multiple tissue antibodies, and/or a specific nonhistone ANA (SS-B)), diabetes mellitus (often characterized, e.g., by cell-mediated and humoral islet cell antibodies), and adrenergic drug resistance (including adrenergic drug resistance with asthma or cystic fibrosis) (often characterized, e.g., by beta-adrenergic receptor antibodies).

[1007] Additional autoimmune disorders (that are possible) that may be treated, prevented, and/or diagnosed with the compositions of the invention include, but are not limited to, chronic active hepatitis (often characterized, e.g., by smooth muscle antibodies), primary biliary cirrhosis (often characterized, e.g., by mitochondrial antibodies), other endocrine gland failure (often characterized, e.g., by specific tissue antibodies in some cases), vitiligo (often characterized, e.g., by melanocyte antibodies), vasculitis (often characterized, e.g., by Ig and complement in vessel walls and/or low serum complement), post-MI (often characterized, e.g., by myocardial antibodies), cardiomyopathy syndrome (often characterized, e.g., by myocardial antibodies), urticaria (often characterized, e.g., by IgG and IgM antibodies to IgE), atopic dermatitis (often characterized, e.g., by IgG and IgM antibodies to IgE), asthma (often characterized, e.g., by IgG and IgM antibodies to IgE), and many other inflammatory, granulomatous, degenerative, and atrophic disorders.

**[1008]** In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prevented, and/or diagnosed using for example, antagonists or agonists, polypeptides or polynucleotides, or antibodies of the present invention.

**[1009]** In a preferred embodiment polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention could be used as an agent to boost immunoresponsiveness among B cell and/or T cell immunodeficient individuals.

**[1010]** B cell immunodeficiencies that may be ameliorated or treated by administering the polypeptides or polynucleotides of the invention, and/or agonists thereof, include, but are not limited to, severe combined immunodeficiency (SCID)-X linked, SCID-autosomal, adenosine deaminase deficiency (ADA deficiency), X-linked agammaglobulinemia (XLA), Bruton's disease, congenital agammaglobulinemia, X-linked infantile agammaglobulinemia, acquired agammaglobulinemia, adult onset agammaglobulinemia, late-onset agammaglobulinemia, dysgammaglobulinemia, hypogammaglobulinemia, transient hypogammaglobulinemia of infancy, unspecified hypogammaglobulinemia, agammaglobulinemia, common variable immunodeficiency (CVI) (acquired), Wiskott-Aldrich Syndrome (WAS), X-linked immunodeficiency with hyper IgM, non X-linked immunodeficiency with hyper IgM, selective IgA deficiency, IgG subclass deficiency (with or without IgA deficiency), antibody deficiency with normal or elevated Igs, immunodeficiency with thymoma, Ig heavy chain deletions, kappa chain deficiency, B cell lymphoproliferative disorder (BLPD), selective IgM immunodeficiency, recessive agammaglobulinemia (Swiss type), reticular dysgenesis, neonatal neutropenia, severe congenital leukopenia, thymic aplasia or dysplasia with immunodeficiency, ataxia-telangiectasia, short limbed dwarfism, X-linked lymphoproliferative syndrome (XLP), Nezelof syndrome-combined immunodeficiency with Igs, purine nucleoside phosphorylase deficiency (PNP), MHC Class II deficiency (Bare Lymphocyte Syndrome) and severe combined immunodeficiency.

**[1011]** T cell deficiencies that may be ameliorated or treated by administering the polypeptides or polynucleotides of the invention, and/or agonists thereof include, but

are not limited to, for example, DiGeorge anomaly, thymic hypoplasia, third and fourth pharyngeal pouch syndrome, 22q11.2 deletion, chronic mucocutaneous candidiasis, natural killer cell deficiency (NK), idiopathic CD4<sup>+</sup> T-lymphocytopenia, immunodeficiency with predominant T cell defect (unspecified), and unspecified immunodeficiency of cell mediated immunity. In specific embodiments, DiGeorge anomaly or conditions associated with DiGeorge anomaly are ameliorated or treated by, for example, administering the polypeptides or polynucleotides of the invention, or antagonists or agonists thereof.

[1012] Other immunodeficiencies that may be ameliorated or treated by administering polypeptides or polynucleotides of the invention, and/or agonists thereof, include, but are not limited to, severe combined immunodeficiency (SCID; e.g., X-linked SCID, autosomal SCID, and adenosine deaminase deficiency), ataxia-telangiectasia, Wiskott-Aldrich syndrome, short-limber dwarfism, X-linked lymphoproliferative syndrome (XLP), Nezelof syndrome (e.g., purine nucleoside phosphorylase deficiency), MHC Class II deficiency. In specific embodiments, ataxia-telangiectasia or conditions associated with ataxia-telangiectasia are ameliorated or treated by administering the polypeptides or polynucleotides of the invention, and/or agonists thereof.

[1013] In a specific preferred embodiment, rheumatoid arthritis is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention. In another specific preferred embodiment, systemic lupus erythematosus is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention. In another specific preferred embodiment, idiopathic thrombocytopenia purpura is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention. In another specific preferred embodiment IgA nephropathy is treated, prevented, and/or diagnosed using polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention. In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and

disorders recited above are treated, prevented, and/or diagnosed using antibodies against the protein of the invention.

**[1014]** Similarly, allergic reactions and conditions, such as asthma (particularly allergic asthma) or other respiratory problems, may also be treated, prevented, and/or diagnosed using polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof. Moreover, these molecules can be used to treat, prevent, and/or diagnose anaphylaxis, hypersensitivity to an antigenic molecule, or blood group incompatibility.

**[1015]** Moreover, inflammatory conditions may also be treated, diagnosed, and/or prevented with polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention. Such inflammatory conditions include, but are not limited to, for example, respiratory disorders (such as, e.g., asthma and allergy); gastrointestinal disorders (such as, e.g., inflammatory bowel disease); cancers (such as, e.g., gastric, ovarian, lung, bladder, liver, and breast); CNS disorders (such as, e.g., multiple sclerosis, blood-brain barrier permeability, ischemic brain injury and/or stroke, traumatic brain injury, neurodegenerative disorders (such as, e.g., Parkinson's disease and Alzheimer's disease), AIDS-related dementia, and prion disease); cardiovascular disorders (such as, e.g., atherosclerosis, myocarditis, cardiovascular disease, and cardiopulmonary bypass complications); as well as many additional diseases, conditions, and disorders that are characterized by inflammation (such as, e.g., chronic hepatitis (B and C), rheumatoid arthritis, gout, trauma, septic shock, pancreatitis, sarcoidosis, dermatitis, renal ischemia-reperfusion injury, Grave's disease, systemic lupus erythematosus, diabetes mellitus (i.e., type 1 diabetes), and allogenic transplant rejection).

**[1016]** In specific embodiments, polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, are useful to treat, diagnose, and/or prevent transplantation rejections, graft-versus-host disease, autoimmune and inflammatory diseases (e.g., immune complex-induced vasculitis, glomerulonephritis, hemolytic anemia, myasthenia gravis, type II collagen-induced arthritis, experimental allergic and hyperacute xenograft rejection, rheumatoid arthritis, and systemic lupus erythematosus (SLE). Organ rejection occurs by host immune cell destruction of the

transplanted tissue through an immune response. Similarly, an immune response is also involved in GVHD, but, in this case, the foreign transplanted immune cells destroy the host tissues. Polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists thereof, that inhibit an immune response, particularly the activation, proliferation, differentiation, or chemotaxis of T-cells, may be an effective therapy in preventing organ rejection or GVHD.

[1017] Similarly, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may also be used to modulate and/or diagnose inflammation. For example, since polypeptides, antibodies, or polynucleotides of the invention, and/or agonists or antagonists of the invention may inhibit the activation, proliferation and/or differentiation of cells involved in an inflammatory response, these molecules can be used to treat, diagnose, or prognose, inflammatory conditions, both chronic and acute conditions, including, but not limited to, inflammation associated with infection (e.g., septic shock, sepsis, or systemic inflammatory response syndrome (SIRS)), ischemia-reperfusion injury, endotoxin lethality, arthritis, complement-mediated hyperacute rejection, nephritis, cytokine or chemokine induced lung injury, inflammatory bowel disease, Crohn's disease, and resulting from over production of cytokines (e.g., TNF or IL-1.).

[1018] Polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the invention can be used to treat, detect, and/or prevent infectious agents. For example, by increasing the immune response, particularly increasing the proliferation activation and/or differentiation of B and/or T cells, infectious diseases may be treated, detected, and/or prevented. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may also directly inhibit the infectious agent (refer to section of application listing infectious agents, etc), without necessarily eliciting an immune response.

[1019] Additional preferred embodiments of the invention include, but are not limited to, the use of polypeptides, antibodies, polynucleotides and/or agonists or antagonists in the following applications:



**[1020]** Administration to an animal (e.g., mouse, rat, rabbit, hamster, guinea pig, pigs, micro-pig, chicken, camel, goat, horse, cow, sheep, dog, cat, non-human primate, and human, most preferably human) to boost the immune system to produce increased quantities of one or more antibodies (e.g., IgG, IgA, IgM, and IgE), to induce higher affinity antibody production (e.g., IgG, IgA, IgM, and IgE), and/or to increase an immune response.

**[1021]** Administration to an animal (including, but not limited to, those listed above, and also including transgenic animals) incapable of producing functional endogenous antibody molecules or having an otherwise compromised endogenous immune system, but which is capable of producing human immunoglobulin molecules by means of a reconstituted or partially reconstituted immune system from another animal (see, e.g., published PCT Application Nos. WO98/24893, WO/9634096, WO/9633735, and WO/9110741).

**[1022]** A vaccine adjuvant that enhances immune responsiveness to specific antigen.

**[1023]** An adjuvant to enhance tumor-specific immune responses.

**[1024]** An adjuvant to enhance anti-viral immune responses. Anti-viral immune responses that may be enhanced using the compositions of the invention as an adjuvant, include virus and virus associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: AIDS, meningitis, Dengue, EBV, and hepatitis (e.g., hepatitis B). In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a virus, disease, or symptom selected from the group consisting of: HIV/AIDS, Respiratory syncytial virus, Dengue, Rotavirus, Japanese B encephalitis, Influenza A and B, Parainfluenza, Measles, Cytomegalovirus, Rabies, Junin, Chikungunya, Rift Valley fever, Herpes simplex, and yellow fever.

**[1025]** An adjuvant to enhance anti-bacterial or anti-fungal immune responses. Anti-bacterial or anti-fungal immune responses that may be enhanced using the compositions of the invention as an adjuvant, include bacteria or fungus and bacteria or fungus associated diseases or symptoms described herein or otherwise known in

the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: tetanus, Diphtheria, botulism, and meningitis type B. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to a bacteria or fungus, disease, or symptom selected from the group consisting of: *Vibrio cholerae*, *Mycobacterium leprae*, *Salmonella typhi*, *Salmonella paratyphi*, *Meisseriesia meningitidis*, *Streptococcus pneumoniae*, Group B streptococcus, *Shigella spp.*, Enterotoxigenic *Escherichia coli*, Enterohemorrhagic *E. coli*, *Borrelia burgdorferi*, and Plasmodium (malaria).

[1026] An adjuvant to enhance anti-parasitic immune responses. Anti-parasitic immune responses that may be enhanced using the compositions of the invention as an adjuvant, include parasite and parasite associated diseases or symptoms described herein or otherwise known in the art. In specific embodiments, the compositions of the invention are used as an adjuvant to enhance an immune response to a parasite. In another specific embodiment, the compositions of the invention are used as an adjuvant to enhance an immune response to Plasmodium (malaria).

[1027] As a stimulator of B cell responsiveness to pathogens.

[1028] As an activator of T cells.

[1029] As an agent that elevates the immune status of an individual prior to their receipt of immunosuppressive therapies.

[1030] As an agent to induce higher affinity antibodies.

[1031] As an agent to increase serum immunoglobulin concentrations.

[1032] As an agent to accelerate recovery of immunocompromised individuals.

[1033] As an agent to boost immunoresponsiveness among aged populations.

[1034] As an immune system enhancer prior to, during, or after bone marrow transplant and/or other transplants (e.g., allogeneic or xenogeneic organ transplantation). With respect to transplantation, compositions of the invention may be administered prior to, concomitant with, and/or after transplantation. In a specific embodiment, compositions of the invention are administered after transplantation, prior to the beginning of recovery of T-cell populations. In another specific

embodiment, compositions of the invention are first administered after transplantation after the beginning of recovery of T cell populations, but prior to full recovery of B cell populations.

**[1035]** As an agent to boost immunoresponsiveness among individuals having an acquired loss of B cell function. Conditions resulting in an acquired loss of B cell function that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, HIV Infection, AIDS, bone marrow transplant, and B cell chronic lymphocytic leukemia (CLL).

**[1036]** As an agent to boost immunoresponsiveness among individuals having a temporary immune deficiency. Conditions resulting in a temporary immune deficiency that may be ameliorated or treated by administering the polypeptides, antibodies, polynucleotides and/or agonists or antagonists thereof, include, but are not limited to, recovery from viral infections (e.g., influenza), conditions associated with malnutrition, recovery from infectious mononucleosis, or conditions associated with stress, recovery from measles, recovery from blood transfusion, recovery from surgery.

**[1037]** As a regulator of antigen presentation by monocytes, dendritic cells, and/or B-cells. In one embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention enhance antigen presentation or antagonizes antigen presentation in vitro or in vivo. Moreover, in related embodiments, said enhancement or antagonization of antigen presentation may be useful as an anti-tumor treatment or to modulate the immune system.

**[1038]** As an agent to direct an individuals immune system towards development of a humoral response (i.e. TH2) as opposed to a TH1 cellular response.

**[1039]** As a means to induce tumor proliferation and thus make it more susceptible to anti-neoplastic agents. For example, multiple myeloma is a slowly dividing disease and is thus refractory to virtually all anti-neoplastic regimens. If these cells were forced to proliferate more rapidly their susceptibility profile would likely change.

**[1040]** As a stimulator of B cell production in pathologies such as AIDS, chronic lymphocyte disorder and/or Common Variable Immunodeficiency.

**[1041]** As a therapy for generation and/or regeneration of lymphoid tissues following surgery, trauma or genetic defect.

**[1042]** As a gene-based therapy for genetically inherited disorders resulting in immuno-incompetence such as observed among SCID patients.

**[1043]** As an antigen for the generation of antibodies to inhibit or enhance immune mediated responses against polypeptides of the invention.

**[1044]** As a means of activating T cells.

**[1045]** As a means of activating monocytes/macrophages to defend against parasitic diseases that effect monocytes such as Leshmania.

**[1046]** As pretreatment of bone marrow samples prior to transplant. Such treatment would increase B cell representation and thus accelerate recover.

**[1047]** As a means of regulating secreted cytokines that are elicited by polypeptides of the invention.

**[1048]** Additionally, polypeptides or polynucleotides of the invention, and/or agonists thereof, may be used to treat or prevent IgE-mediated allergic reactions. Such allergic reactions include, but are not limited to, asthma, rhinitis, and eczema.

**[1049]** All of the above described applications as they may apply to veterinary medicine.

**[1050]** Antagonists of the invention include, for example, binding and/or inhibitory antibodies, antisense nucleic acids, or ribozymes. These would be expected to reverse many of the activities of the ligand described above as well as find clinical or practical application as:

**[1051]** A means of blocking various aspects of immune responses to foreign agents or self. Examples include autoimmune disorders such as lupus, and arthritis, as well as immunoresponsiveness to skin allergies, inflammation, bowel disease, injury and pathogens.

**[1052]** A therapy for preventing the B cell proliferation and Ig secretion associated with autoimmune diseases such as idiopathic thrombocytopenic purpura, systemic lupus erythramatosus and MS.

**[1053]** An inhibitor of B and/or T cell migration in endothelial cells. This activity disrupts tissue architecture or cognate responses and is useful, for example in disrupting immune responses, and blocking sepsis.

**[1054]** An inhibitor of graft versus host disease or transplant rejection.

**[1055]** A therapy for B cell and/or T cell malignancies such as ALL, Hodgkins disease, non-Hodgkins lymphoma, Chronic lymphocyte leukemia, plasmacytomas, multiple myeloma, Burkitt's lymphoma, and EBV-transformed diseases.

**[1056]** A therapy for chronic hypergammaglobulinemia evident in such diseases as monoclonal gammopathy of undetermined significance (MGUS), Waldenstrom's disease, related idiopathic monoclonal gammopathies, and plasmacytomas.

**[1057]** A therapy for decreasing cellular proliferation of Large B-cell Lymphomas.

**[1058]** A means of decreasing the involvement of B cells and Ig associated with Chronic Myelogenous Leukemia.

**[1059]** An immunosuppressive agent(s).

**[1060]** Polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to modulate IgE concentrations in vitro or in vivo.

**[1061]** In another embodiment, administration of polypeptides, antibodies, polynucleotides and/or agonists or antagonists of the invention, may be used to treat or prevent IgE-mediated allergic reactions including, but not limited to, asthma, rhinitis, and eczema.

**[1062]** The agonists and antagonists may be employed in a composition with a pharmaceutically acceptable carrier, e.g., as described herein.

**[1063]** The agonists or antagonists may be employed for instance to inhibit polypeptide chemotaxis and activation of macrophages and their precursors, and of neutrophils, basophils, B lymphocytes and some T-cell subsets, e.g., activated and CD8 cytotoxic T cells and natural killer cells, in certain auto-immune and chronic inflammatory and infective diseases. Examples of autoimmune diseases are described herein and include multiple sclerosis, and insulin-dependent diabetes. The antagonists or agonists may also be employed to treat infectious diseases including silicosis, sarcoidosis, idiopathic pulmonary fibrosis by, for example, preventing the recruitment and activation of mononuclear phagocytes. They may also be employed

to treat idiopathic hyper-eosinophilic syndrome by, for example, preventing eosinophil production and migration. The antagonists or agonists or may also be employed for treating atherosclerosis, for example, by preventing monocyte infiltration in the artery wall.

[1064] Antibodies against polypeptides of the invention may be employed to treat ARDS.

[1065] Agonists and/or antagonists of the invention also have uses in stimulating wound and tissue repair, stimulating angiogenesis, stimulating the repair of vascular or lymphatic diseases or disorders. Additionally, agonists and antagonists of the invention may be used to stimulate the regeneration of mucosal surfaces.

[1066] In a specific embodiment, polynucleotides or polypeptides, and/or agonists thereof are used to treat or prevent a disorder characterized by primary or acquired immunodeficiency, deficient serum immunoglobulin production, recurrent infections, and/or immune system dysfunction. Moreover, polynucleotides or polypeptides, and/or agonists thereof may be used to treat or prevent infections of the joints, bones, skin, and/or parotid glands, blood-borne infections (e.g., sepsis, meningitis, septic arthritis, and/or osteomyelitis), autoimmune diseases (e.g., those disclosed herein), inflammatory disorders, and malignancies, and/or any disease or disorder or condition associated with these infections, diseases, disorders and/or malignancies) including, but not limited to, CVID, other primary immune deficiencies, HIV disease, CLL, recurrent bronchitis, sinusitis, otitis media, conjunctivitis, pneumonia, hepatitis, meningitis, herpes zoster (e.g., severe herpes zoster), and/or pneumocystis carinii.

[1067] In another embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention are used to treat, and/or diagnose an individual having common variable immunodeficiency disease ("CVID"; also known as "acquired agammaglobulinemia" and "acquired hypogammaglobulinemia") or a subset of this disease.

[1068] In a specific embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to treat, diagnose, and/or prevent (1) cancers or neoplasms and (2) autoimmune cell or tissue-related cancers or neoplasms. In a preferred embodiment, polynucleotides, polypeptides, antibodies,

and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat, diagnose, and/or prevent acute myelogenous leukemia. In a further preferred embodiment, polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention conjugated to a toxin or a radioactive isotope, as described herein, may be used to treat, diagnose, and/or prevent, chronic myelogenous leukemia, multiple myeloma, non-Hodgkins lymphoma, and/or Hodgkins disease.

[1069] In another specific embodiment, polynucleotides or polypeptides, and/or agonists or antagonists of the invention may be used to treat, diagnose, prognose, and/or prevent selective IgA deficiency, myeloperoxidase deficiency, C2 deficiency, ataxia-telangiectasia, DiGeorge anomaly, common variable immunodeficiency (CVI), X-linked agammaglobulinemia, severe combined immunodeficiency (SCID), chronic granulomatous disease (CGD), and Wiskott-Aldrich syndrome.

[1070] Examples of autoimmune disorders that can be treated or detected are described above and also include, but are not limited to: Addison's Disease, hemolytic anemia, antiphospholipid syndrome, rheumatoid arthritis, dermatitis, allergic encephalomyelitis, glomerulonephritis, Goodpasture's Syndrome, Graves' Disease, Multiple Sclerosis, Myasthenia Gravis, Neuritis, Ophthalmia, Bullous Pemphigoid, Pemphigus, Polyendocrinopathies, Purpura, Reiter's Disease, Stiff-Man Syndrome, Autoimmune Thyroiditis, Systemic Lupus Erythematosus, Autoimmune Pulmonary Inflammation, Guillain-Barre Syndrome, insulin dependent diabetes mellitus, and autoimmune inflammatory eye disease.

[1071] In a preferred embodiment, the autoimmune diseases and disorders and/or conditions associated with the diseases and disorders recited above are treated, prognosed, prevented, and/or diagnosed using antibodies against the polypeptide of the invention.

[1072] As an agent to boost immunoresponsiveness among B cell immunodeficient individuals, such as, for example, an individual who has undergone a partial or complete splenectomy.

[1073] Additionally, polynucleotides, polypeptides, and/or antagonists of the invention may affect apoptosis, and therefore, would be useful in treating a number of

diseases associated with increased cell survival or the inhibition of apoptosis. For example, diseases associated with increased cell survival or the inhibition of apoptosis that could be treated or detected by polynucleotides, polypeptides, and/or antagonists of the invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection. In preferred embodiments, polynucleotides, polypeptides, and/or antagonists of the invention are used to inhibit growth, progression, and/or metastasis of cancers, in particular those listed above.

[1074] Additional diseases or conditions associated with increased cell survival that could be treated or detected by polynucleotides, polypeptides, and/or antagonists of the invention, include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic



cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

**[1075]** Diseases associated with increased apoptosis that could be treated or detected by polynucleotides, polypeptides, and/or antagonists of the invention, include AIDS; neurodegenerative disorders (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune disorders (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

**[1076]** Hyperproliferative diseases and/or disorders that could be detected and/or treated by polynucleotides, polypeptides, and/or antagonists of the invention, include, but are not limited to neoplasms located in the: liver, abdomen, bone, breast, digestive system, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

**[1077]** Similarly, other hyperproliferative disorders can also be treated or detected by polynucleotides, polypeptides, and/or antagonists of the invention. Examples of such

hyperproliferative disorders include, but are not limited to:

hypergammaglobulinemia, lymphoproliferative disorders, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenström's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

**[1078] Hyperproliferative Disorders**

**[1079]** A polynucleotides or polypeptides, or agonists or antagonists of the invention can be used to treat, prevent, and/or diagnose hyperproliferative diseases, disorders, and/or conditions, including neoplasms. A polynucleotides or polypeptides, or agonists or antagonists of the present invention may inhibit the proliferation of the disorder through direct or indirect interactions. Alternatively, a polynucleotides or polypeptides, or agonists or antagonists of the present invention may proliferate other cells which can inhibit the hyperproliferative disorder.

**[1080]** For example, by increasing an immune response, particularly increasing antigenic qualities of the hyperproliferative disorder or by proliferating, differentiating, or mobilizing T-cells, hyperproliferative diseases, disorders, and/or conditions can be treated, prevented, and/or diagnosed. This immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, decreasing an immune response may also be a method of treating, preventing, and/or diagnosing hyperproliferative diseases, disorders, and/or conditions, such as a chemotherapeutic agent.

**[1081]** Examples of hyperproliferative diseases, disorders, and/or conditions that can be treated, prevented, and/or diagnosed by polynucleotides or polypeptides, or agonists or antagonists of the present invention include, but are not limited to neoplasms located in the: colon, abdomen, bone, breast, digestive system, liver, pancreas, peritoneum, endocrine glands (adrenal, parathyroid, pituitary, testicles, ovary, thymus, thyroid), eye, head and neck, nervous (central and peripheral), lymphatic system, pelvic, skin, soft tissue, spleen, thoracic, and urogenital.

**[1082]** Similarly, other hyperproliferative diseases, disorders, and/or conditions can also be treated, prevented, and/or diagnosed by a polynucleotides or polypeptides, or

agonists or antagonists of the present invention. Examples of such hyperproliferative diseases, disorders, and/or conditions include, but are not limited to: hypergammaglobulinemia, lymphoproliferative diseases, disorders, and/or conditions, paraproteinemias, purpura, sarcoidosis, Sezary Syndrome, Waldenström's Macroglobulinemia, Gaucher's Disease, histiocytosis, and any other hyperproliferative disease, besides neoplasia, located in an organ system listed above.

[1083] One preferred embodiment utilizes polynucleotides of the present invention to inhibit aberrant cellular division, by gene therapy using the present invention, and/or protein fusions or fragments thereof.

[1084] Thus, the present invention provides a method for treating or preventing cell proliferative diseases, disorders, and/or conditions by inserting into an abnormally proliferating cell a polynucleotide of the present invention, wherein said polynucleotide represses said expression.

[1085] Another embodiment of the present invention provides a method of treating or preventing cell-proliferative diseases, disorders, and/or conditions in individuals comprising administration of one or more active gene copies of the present invention to an abnormally proliferating cell or cells. In a preferred embodiment, polynucleotides of the present invention is a DNA construct comprising a recombinant expression vector effective in expressing a DNA sequence encoding said polynucleotides. In another preferred embodiment of the present invention, the DNA construct encoding the polynucleotides of the present invention is inserted into cells to be treated utilizing a retrovirus, or more preferably an adenoviral vector (See G J. Nabel, et. al., PNAS 1999 96: 324-326, which is hereby incorporated by reference). In a most preferred embodiment, the viral vector is defective and will not transform non-proliferating cells, only proliferating cells. Moreover, in a preferred embodiment, the polynucleotides of the present invention inserted into proliferating cells either alone, or in combination with or fused to other polynucleotides, can then be modulated via an external stimulus (i.e. magnetic, specific small molecule, chemical, or drug administration, etc.), which acts upon the promoter upstream of said polynucleotides to induce expression of the encoded protein product. As such the beneficial therapeutic affect of the present invention may be expressly modulated (i.e.

to increase, decrease, or inhibit expression of the present invention) based upon said external stimulus.

**[1086]** Polynucleotides of the present invention may be useful in repressing expression of oncogenic genes or antigens. By "repressing expression of the oncogenic genes " is intended the suppression of the transcription of the gene, the degradation of the gene transcript (pre-message RNA), the inhibition of splicing, the destruction of the messenger RNA, the prevention of the post-translational modifications of the protein, the destruction of the protein, or the inhibition of the normal function of the protein.

**[1087]** For local administration to abnormally proliferating cells, polynucleotides of the present invention may be administered by any method known to those of skill in the art including, but not limited to transfection, electroporation, microinjection of cells, or in vehicles such as liposomes, lipofectin, or as naked polynucleotides, or any other method described throughout the specification. The polynucleotide of the present invention may be delivered by known gene delivery systems such as, but not limited to, retroviral vectors (Gilboa, J. Virology 44:845 (1982); Hocke, Nature 320:275 (1986); Wilson, et al., Proc. Natl. Acad. Sci. U.S.A. 85:3014), vaccinia virus system (Chakrabarty et al., Mol. Cell Biol. 5:3403 (1985) or other efficient DNA delivery systems (Yates et al., Nature 313:812 (1985)) known to those skilled in the art. These references are exemplary only and are hereby incorporated by reference. In order to specifically deliver or transfect cells which are abnormally proliferating and spare non-dividing cells, it is preferable to utilize a retrovirus, or adenoviral (as described in the art and elsewhere herein) delivery system known to those of skill in the art. Since host DNA replication is required for retroviral DNA to integrate and the retrovirus will be unable to self replicate due to the lack of the retrovirus genes needed for its life cycle. Utilizing such a retroviral delivery system for polynucleotides of the present invention will target said gene and constructs to abnormally proliferating cells and will spare the non-dividing normal cells.

**[1088]** The polynucleotides of the present invention may be delivered directly to cell proliferative disorder/disease sites in internal organs, body cavities and the like by use of imaging devices used to guide an injecting needle directly to the disease site. The

polynucleotides of the present invention may also be administered to disease sites at the time of surgical intervention.

**[1089]** By "cell proliferative disease" is meant any human or animal disease or disorder, affecting any one or any combination of organs, cavities, or body parts, which is characterized by single or multiple local abnormal proliferations of cells, groups of cells, or tissues, whether benign or malignant.

**[1090]** Any amount of the polynucleotides of the present invention may be administered as long as it has a biologically inhibiting effect on the proliferation of the treated cells. Moreover, it is possible to administer more than one of the polynucleotide of the present invention simultaneously to the same site. By "biologically inhibiting" is meant partial or total growth inhibition as well as decreases in the rate of proliferation or growth of the cells. The biologically inhibitory dose may be determined by assessing the effects of the polynucleotides of the present invention on target malignant or abnormally proliferating cell growth in tissue culture, tumor growth in animals and cell cultures, or any other method known to one of ordinary skill in the art.

**[1091]** The present invention is further directed to antibody-based therapies which involve administering of anti-polypeptides and anti-polynucleotide antibodies to a mammalian, preferably human, patient for treating, preventing, and/or diagnosing one or more of the described diseases, disorders, and/or conditions. Methods for producing anti-polypeptides and anti-polynucleotide antibodies polyclonal and monoclonal antibodies are described in detail elsewhere herein. Such antibodies may be provided in pharmaceutically acceptable compositions as known in the art or as described herein.

**[1092]** A summary of the ways in which the antibodies of the present invention may be used therapeutically includes binding polynucleotides or polypeptides of the present invention locally or systemically in the body or by direct cytotoxicity of the antibody, e.g. as mediated by complement (CDC) or by effector cells (ADCC). Some of these approaches are described in more detail below. Armed with the teachings provided herein, one of ordinary skill in the art will know how to use the antibodies of

the present invention for diagnostic, monitoring or therapeutic purposes without undue experimentation.

[1093] In particular, the antibodies, fragments and derivatives of the present invention are useful for treating, preventing, and/or diagnosing a subject having or developing cell proliferative and/or differentiation diseases, disorders, and/or conditions as described herein. Such treatment comprises administering a single or multiple doses of the antibody, or a fragment, derivative, or a conjugate thereof.

[1094] The antibodies of this invention may be advantageously utilized in combination with other monoclonal or chimeric antibodies, or with lymphokines or hematopoietic growth factors, for example, which serve to increase the number or activity of effector cells which interact with the antibodies.

[1095] It is preferred to use high affinity and/or potent in vivo inhibiting and/or neutralizing antibodies against polypeptides or polynucleotides of the present invention, fragments or regions thereof, for both immunoassays directed to and therapy of diseases, disorders, and/or conditions related to polynucleotides or polypeptides, including fragments thereof, of the present invention. Such antibodies, fragments, or regions, will preferably have an affinity for polynucleotides or polypeptides, including fragments thereof. Preferred binding affinities include those with a dissociation constant or  $K_d$  less than  $5 \times 10^{-6}M$ ,  $10^{-6}M$ ,  $5 \times 10^{-7}M$ ,  $10^{-7}M$ ,  $5 \times 10^{-8}M$ ,  $10^{-8}M$ ,  $5 \times 10^{-9}M$ ,  $10^{-9}M$ ,  $5 \times 10^{-10}M$ ,  $10^{-10}M$ ,  $5 \times 10^{-11}M$ ,  $10^{-11}M$ ,  $5 \times 10^{-12}M$ ,  $10^{-12}M$ ,  $5 \times 10^{-13}M$ ,  $10^{-13}M$ ,  $5 \times 10^{-14}M$ ,  $10^{-14}M$ ,  $5 \times 10^{-15}M$ , and  $10^{-15}M$ .

[1096] Moreover, polypeptides of the present invention are useful in inhibiting the angiogenesis of proliferative cells or tissues, either alone, as a protein fusion, or in combination with other polypeptides directly or indirectly, as described elsewhere herein. In a most preferred embodiment, said anti-angiogenesis effect may be achieved indirectly, for example, through the inhibition of hematopoietic, tumor-specific cells, such as tumor-associated macrophages (See Joseph IB, et al. J Natl Cancer Inst, 90(21):1648-53 (1998), which is hereby incorporated by reference). Antibodies directed to polypeptides or polynucleotides of the present invention may also result in inhibition of angiogenesis directly, or indirectly (See Witte L, et al.,

Cancer Metastasis Rev. 17(2):155-61 (1998), which is hereby incorporated by reference)).

[1097] Polypeptides, including protein fusions, of the present invention, or fragments thereof may be useful in inhibiting proliferative cells or tissues through the induction of apoptosis. Said polypeptides may act either directly, or indirectly to induce apoptosis of proliferative cells and tissues, for example in the activation of a death-domain receptor, such as tumor necrosis factor (TNF) receptor-1, CD95 (Fas/APO-1), TNF-receptor-related apoptosis-mediated protein (TRAMP) and TNF-related apoptosis-inducing ligand (TRAIL) receptor-1 and -2 (See Schulze-Osthoff K, et.al., Eur J Biochem 254(3):439-59 (1998), which is hereby incorporated by reference). Moreover, in another preferred embodiment of the present invention, said polypeptides may induce apoptosis through other mechanisms, such as in the activation of other proteins which will activate apoptosis, or through stimulating the expression of said proteins, either alone or in combination with small molecule drugs or adjuvants, such as apoptonin, galectins, thioredoxins, antiinflammatory proteins (See for example, Mutat Res 400(1-2):447-55 (1998), Med Hypotheses.50(5):423-33 (1998), Chem Biol Interact. Apr 24;111-112:23-34 (1998), J Mol Med.76(6):402-12 (1998), Int J Tissue React;20(1):3-15 (1998), which are all hereby incorporated by reference).

[1098] Polypeptides, including protein fusions to, or fragments thereof, of the present invention are useful in inhibiting the metastasis of proliferative cells or tissues. Inhibition may occur as a direct result of administering polypeptides, or antibodies directed to said polypeptides as described elsewhere herein, or indirectly, such as activating the expression of proteins known to inhibit metastasis, for example alpha 4 integrins, (See, e.g., Curr Top Microbiol Immunol 1998;231:125-41, which is hereby incorporated by reference). Such therapeutic affects of the present invention may be achieved either alone, or in combination with small molecule drugs or adjuvants.

[1099] In another embodiment, the invention provides a method of delivering compositions containing the polypeptides of the invention (e.g., compositions containing polypeptides or polypeptide antibodies associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs) to targeted cells

expressing the polypeptide of the present invention. Polypeptides or polypeptide antibodies of the invention may be associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions.

[1100] Polypeptides, protein fusions to, or fragments thereof, of the present invention are useful in enhancing the immunogenicity and/or antigenicity of proliferating cells or tissues, either directly, such as would occur if the polypeptides of the present invention 'vaccinated' the immune response to respond to proliferative antigens and immunogens, or indirectly, such as in activating the expression of proteins known to enhance the immune response (e.g. chemokines), to said antigens and immunogens.

**[1101] Cardiovascular Disorders**

[1102] Polynucleotides or polypeptides, or agonists or antagonists of the invention may be used to treat, prevent, and/or diagnose cardiovascular diseases, disorders, and/or conditions, including peripheral artery disease, such as limb ischemia.

[1103] Cardiovascular diseases, disorders, and/or conditions include cardiovascular abnormalities, such as arterio-arterial fistula, arteriovenous fistula, cerebral arteriovenous malformations, congenital heart defects, pulmonary atresia, and Scimitar Syndrome. Congenital heart defects include aortic coarctation, cor triatriatum, coronary vessel anomalies, crisscross heart, dextrocardia, patent ductus arteriosus, Ebstein's anomaly, Eisenmenger complex, hypoplastic left heart syndrome, levocardia, tetralogy of fallot, transposition of great vessels, double outlet right ventricle, tricuspid atresia, persistent truncus arteriosus, and heart septal defects, such as aortopulmonary septal defect, endocardial cushion defects, Lutembacher's Syndrome, trilog of Fallot, ventricular heart septal defects.

[1104] Cardiovascular diseases, disorders, and/or conditions also include heart disease, such as arrhythmias, carcinoid heart disease, high cardiac output, low cardiac output, cardiac tamponade, endocarditis (including bacterial), heart aneurysm, cardiac arrest, congestive heart failure, congestive cardiomyopathy, paroxysmal dyspnea, cardiac edema, heart hypertrophy, congestive cardiomyopathy, left ventricular hypertrophy, right ventricular hypertrophy, post-infarction heart rupture, ventricular



septal rupture, heart valve diseases, myocardial diseases, myocardial ischemia, pericardial effusion, pericarditis (including constrictive and tuberculous), pneumopericardium, postpericardiotomy syndrome, pulmonary heart disease, rheumatic heart disease, ventricular dysfunction, hyperemia, cardiovascular pregnancy complications, Scimitar Syndrome, cardiovascular syphilis, and cardiovascular tuberculosis.

[1105] Arrhythmias include sinus arrhythmia, atrial fibrillation, atrial flutter, bradycardia, extrasystole, Adams-Stokes Syndrome, bundle-branch block, sinoatrial block, long QT syndrome, parasystole, Lown-Ganong-Levine Syndrome, Mahaim-type pre-excitation syndrome, Wolff-Parkinson-White syndrome, sick sinus syndrome, tachycardias, and ventricular fibrillation. Tachycardias include paroxysmal tachycardia, supraventricular tachycardia, accelerated idioventricular rhythm, atrioventricular nodal reentry tachycardia, ectopic atrial tachycardia, ectopic junctional tachycardia, sinoatrial nodal reentry tachycardia, sinus tachycardia, Torsades de Pointes, and ventricular tachycardia.

[1106] Heart valve disease include aortic valve insufficiency, aortic valve stenosis, hear murmurs, aortic valve prolapse, mitral valve prolapse, tricuspid valve prolapse, mitral valve insufficiency, mitral valve stenosis, pulmonary atresia, pulmonary valve insufficiency, pulmonary valve stenosis, tricuspid atresia, tricuspid valve insufficiency, and tricuspid valve stenosis.

[1107] Myocardial diseases include alcoholic cardiomyopathy, congestive cardiomyopathy, hypertrophic cardiomyopathy, aortic subvalvular stenosis, pulmonary subvalvular stenosis, restrictive cardiomyopathy, Chagas cardiomyopathy, endocardial fibroelastosis, endomyocardial fibrosis, Kearns Syndrome, myocardial reperfusion injury, and myocarditis.

[1108] Myocardial ischemias include coronary disease, such as angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary thrombosis, coronary vasospasm, myocardial infarction and myocardial stunning.

[1109] Cardiovascular diseases also include vascular diseases such as aneurysms, angiodysplasia, angiomas, bacillary angiomas, Hippiel-Lindau Disease, Klippel-Trenaunay-Weber Syndrome, Sturge-Weber Syndrome, angioneurotic edema,

aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular diseases, disorders, and/or conditions, diabetic angiopathies, diabetic retinopathy, embolisms, thrombosis, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal vein occlusion, Scimitar syndrome, superior vena cava syndrome, telangiectasia, atacia telangiectasia, hereditary hemorrhagic telangiectasia, varicocele, varicose veins, varicose ulcer, vasculitis, and venous insufficiency.

**[1110]** Aneurysms include dissecting aneurysms, false aneurysms, infected aneurysms, ruptured aneurysms, aortic aneurysms, cerebral aneurysms, coronary aneurysms, heart aneurysms, and iliac aneurysms.

**[1111]** Arterial occlusive diseases include arteriosclerosis, intermittent claudication, carotid stenosis, fibromuscular dysplasias, mesenteric vascular occlusion, Moyamoya disease, renal artery obstruction, retinal artery occlusion, and thromboangiitis obliterans.

**[1112]** Cerebrovascular diseases, disorders, and/or conditions include carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral embolism and thrombosis, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subarachnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular leukomalacia, vascular headache, cluster headache, migraine, and vertebrobasilar insufficiency.

**[1113]** Embolisms include air embolisms, amniotic fluid embolisms, cholesterol embolisms, blue toe syndrome, fat embolisms, pulmonary embolisms, and thromboembolisms. Thrombosis include coronary thrombosis, hepatic vein thrombosis, retinal vein occlusion, carotid artery thrombosis, sinus thrombosis, Wallenberg's syndrome, and thrombophlebitis.

**[1114]** Ischemia includes cerebral ischemia, ischemic colitis, compartment syndromes, anterior compartment syndrome, myocardial ischemia, reperfusion

injuries, and peripheral limb ischemia. Vasculitis includes aortitis, arteritis, Behcet's Syndrome, Churg-Strauss Syndrome, mucocutaneous lymph node syndrome, thromboangiitis obliterans, hypersensitivity vasculitis, Schoenlein-Henoch purpura, allergic cutaneous vasculitis, and Wegener's granulomatosis.

[1115] Polynucleotides or polypeptides, or agonists or antagonists of the invention, are especially effective for the treatment of critical limb ischemia and coronary disease.

[1116] Polypeptides may be administered using any method known in the art, including, but not limited to, direct needle injection at the delivery site, intravenous injection, topical administration, catheter infusion, biolistic injectors, particle accelerators, gelfoam sponge depots, other commercially available depot materials, osmotic pumps, oral or suppository solid pharmaceutical formulations, decanting or topical applications during surgery, aerosol delivery. Such methods are known in the art. Polypeptides of the invention may be administered as part of a *Therapeutic*, described in more detail below. Methods of delivering polynucleotides of the invention are described in more detail herein.

[1117] **Anti-Angiogenesis Activity**

[1118] The naturally occurring balance between endogenous stimulators and inhibitors of angiogenesis is one in which inhibitory influences predominate. Rastinejad *et al.*, *Cell* 56:345-355 (1989). In those rare instances in which neovascularization occurs under normal physiological conditions, such as wound healing, organ regeneration, embryonic development, and female reproductive processes, angiogenesis is stringently regulated and spatially and temporally delimited. Under conditions of pathological angiogenesis such as that characterizing solid tumor growth, these regulatory controls fail. Unregulated angiogenesis becomes pathologic and sustains progression of many neoplastic and non-neoplastic diseases. A number of serious diseases are dominated by abnormal neovascularization including solid tumor growth and metastases, arthritis, some types of eye diseases, disorders, and/or conditions, and psoriasis. See, e.g., reviews by Moses *et al.*, *Biotech.* 9:630-634 (1991); Folkman *et al.*, *N. Engl. J. Med.*, 333:1757-1763 (1995);

Auerbach *et al.*, *J. Microvasc. Res.* 29:401-411 (1985); Folkman, *Advances in Cancer Research*, eds. Klein and Weinhouse, Academic Press, New York, pp. 175-203 (1985); Patz, *Am. J. Ophthalmol.* 94:715-743 (1982); and Folkman *et al.*, *Science* 221:719-725 (1983). In a number of pathological conditions, the process of angiogenesis contributes to the disease state. For example, significant data have accumulated which suggest that the growth of solid tumors is dependent on angiogenesis. Folkman and Klagsbrun, *Science* 235:442-447 (1987).

[1119] The present invention provides for treatment of diseases, disorders, and/or conditions associated with neovascularization by administration of the polynucleotides and/or polypeptides of the invention, as well as agonists or antagonists of the present invention. Malignant and metastatic conditions which can be treated with the polynucleotides and polypeptides, or agonists or antagonists of the invention include, but are not limited to, malignancies, solid tumors, and cancers described herein and otherwise known in the art (for a review of such disorders, see Fishman *et al.*, *Medicine*, 2d Ed., J. B. Lippincott Co., Philadelphia (1985)). Thus, the present invention provides a method of treating, preventing, and/or diagnosing an angiogenesis-related disease and/or disorder, comprising administering to an individual in need thereof a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist of the invention. For example, polynucleotides, polypeptides, antagonists and/or agonists may be utilized in a variety of additional methods in order to therapeutically treat or prevent a cancer or tumor. Cancers which may be treated, prevented, and/or diagnosed with polynucleotides, polypeptides, antagonists and/or agonists include, but are not limited to solid tumors, including prostate, lung, breast, ovarian, stomach, pancreas, larynx, esophagus, testes, liver, parotid, biliary tract, colon, rectum, cervix, uterus, endometrium, kidney, bladder, thyroid cancer; primary tumors and metastases; melanomas; glioblastoma; Kaposi's sarcoma; leiomyosarcoma; non-small cell lung cancer; colorectal cancer; advanced malignancies; and blood born tumors such as leukemias. For example, polynucleotides, polypeptides, antagonists and/or agonists may be delivered topically, in order to treat or prevent cancers such as skin cancer, head and neck tumors, breast tumors, and Kaposi's sarcoma.

[1120] Within yet other aspects, polynucleotides, polypeptides, antagonists and/or agonists may be utilized to treat superficial forms of bladder cancer by, for example, intravesical administration. Polynucleotides, polypeptides, antagonists and/or agonists may be delivered directly into the tumor, or near the tumor site, via injection or a catheter. Of course, as the artisan of ordinary skill will appreciate, the appropriate mode of administration will vary according to the cancer to be treated. Other modes of delivery are discussed herein.

[1121] Polynucleotides, polypeptides, antagonists and/or agonists may be useful in treating, preventing, and/or diagnosing other diseases, disorders, and/or conditions, besides cancers, which involve angiogenesis. These diseases, disorders, and/or conditions include, but are not limited to: benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas; arteriosclerotic plaques; ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, uveitis and Pterygia (abnormal blood vessel growth) of the eye; rheumatoid arthritis; psoriasis; delayed wound healing; endometriosis; vasculogenesis; granulations; hypertrophic scars (keloids); nonunion fractures; scleroderma; trachoma; vascular adhesions; myocardial angiogenesis; coronary collaterals; cerebral collaterals; arteriovenous malformations; ischemic limb angiogenesis; Osler-Webber Syndrome; plaque neovascularization; telangiectasia; hemophilic joints; angiofibroma; fibromuscular dysplasia; wound granulation; Crohn's disease; and atherosclerosis.

[1122] For example, within one aspect of the present invention methods are provided for treating, preventing, and/or diagnosing hypertrophic scars and keloids, comprising the step of administering a polynucleotide, polypeptide, antagonist and/or agonist of the invention to a hypertrophic scar or keloid.

[1123] Within one embodiment of the present invention polynucleotides, polypeptides, antagonists and/or agonists are directly injected into a hypertrophic scar or keloid, in order to prevent the progression of these lesions. This therapy is of particular value in the prophylactic treatment of conditions which are known to result in the development of hypertrophic scars and keloids (e.g., burns), and is preferably

initiated after the proliferative phase has had time to progress (approximately 14 days after the initial injury), but before hypertrophic scar or keloid development. As noted above, the present invention also provides methods for treating, preventing, and/or diagnosing neovascular diseases of the eye, including for example, corneal neovascularization, neovascular glaucoma, proliferative diabetic retinopathy, retrolental fibroplasia and macular degeneration.

[1124] Moreover, Ocular diseases, disorders, and/or conditions associated with neovascularization which can be treated, prevented, and/or diagnosed with the polynucleotides and polypeptides of the present invention (including agonists and/or antagonists) include, but are not limited to: neovascular glaucoma, diabetic retinopathy, retinoblastoma, retrolental fibroplasia, uveitis, retinopathy of prematurity macular degeneration, corneal graft neovascularization, as well as other eye inflammatory diseases, ocular tumors and diseases associated with choroidal or iris neovascularization. See, e.g., reviews by Waltman *et al.*, *Am. J. Ophthalmol.* 85:704-710 (1978) and Gartner *et al.*, *Surv. Ophthalmol.* 22:291-312 (1978).

[1125] Thus, within one aspect of the present invention methods are provided for treating or preventing neovascular diseases of the eye such as corneal neovascularization (including corneal graft neovascularization), comprising the step of administering to a patient a therapeutically effective amount of a compound (as described above) to the cornea, such that the formation of blood vessels is inhibited. Briefly, the cornea is a tissue which normally lacks blood vessels. In certain pathological conditions however, capillaries may extend into the cornea from the pericorneal vascular plexus of the limbus. When the cornea becomes vascularized, it also becomes clouded, resulting in a decline in the patient's visual acuity. Visual loss may become complete if the cornea completely opacitates. A wide variety of diseases, disorders, and/or conditions can result in corneal neovascularization, including for example, corneal infections (e.g., trachoma, herpes simplex keratitis, leishmaniasis and onchocerciasis), immunological processes (e.g., graft rejection and Stevens-Johnson's syndrome), alkali burns, trauma, inflammation (of any cause), toxic and nutritional deficiency states, and as a complication of wearing contact lenses.

[1126] Within particularly preferred embodiments of the invention, may be prepared for topical administration in saline (combined with any of the preservatives and antimicrobial agents commonly used in ocular preparations), and administered in eyedrop form. The solution or suspension may be prepared in its pure form and administered several times daily. Alternatively, anti-angiogenic compositions, prepared as described above, may also be administered directly to the cornea. Within preferred embodiments, the anti-angiogenic composition is prepared with a muco-adhesive polymer which binds to cornea. Within further embodiments, the anti-angiogenic factors or anti-angiogenic compositions may be utilized as an adjunct to conventional steroid therapy. Topical therapy may also be useful prophylactically in corneal lesions which are known to have a high probability of inducing an angiogenic response (such as chemical burns). In these instances the treatment, likely in combination with steroids, may be instituted immediately to help prevent subsequent complications.

[1127] Within other embodiments, the compounds described above may be injected directly into the corneal stroma by an ophthalmologist under microscopic guidance. The preferred site of injection may vary with the morphology of the individual lesion, but the goal of the administration would be to place the composition at the advancing front of the vasculature (i.e., interspersed between the blood vessels and the normal cornea). In most cases this would involve perilimbic corneal injection to "protect" the cornea from the advancing blood vessels. This method may also be utilized shortly after a corneal insult in order to prophylactically prevent corneal neovascularization. In this situation the material could be injected in the perilimbic cornea interspersed between the corneal lesion and its undesired potential limbic blood supply. Such methods may also be utilized in a similar fashion to prevent capillary invasion of transplanted corneas. In a sustained-release form injections might only be required 2-3 times per year. A steroid could also be added to the injection solution to reduce inflammation resulting from the injection itself.

[1128] Within another aspect of the present invention, methods are provided for treating or preventing neovascular glaucoma, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide,

antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. In one embodiment, the compound may be administered topically to the eye in order to treat or prevent early forms of neovascular glaucoma. Within other embodiments, the compound may be implanted by injection into the region of the anterior chamber angle. Within other embodiments, the compound may also be placed in any location such that the compound is continuously released into the aqueous humor. Within another aspect of the present invention, methods are provided for treating or preventing proliferative diabetic retinopathy, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eyes, such that the formation of blood vessels is inhibited.

[1129] Within particularly preferred embodiments of the invention, proliferative diabetic retinopathy may be treated by injection into the aqueous humor or the vitreous, in order to increase the local concentration of the polynucleotide, polypeptide, antagonist and/or agonist in the retina. Preferably, this treatment should be initiated prior to the acquisition of severe disease requiring photocoagulation.

[1130] Within another aspect of the present invention, methods are provided for treating or preventing retrolental fibroplasia, comprising the step of administering to a patient a therapeutically effective amount of a polynucleotide, polypeptide, antagonist and/or agonist to the eye, such that the formation of blood vessels is inhibited. The compound may be administered topically, via intravitreal injection and/or via intraocular implants.

[1131] Additionally, diseases, disorders, and/or conditions which can be treated, prevented, and/or diagnosed with the polynucleotides, polypeptides, agonists and/or antagonists include, but are not limited to, hemangioma, arthritis, psoriasis, angiofibroma, atherosclerotic plaques, delayed wound healing, granulations, hemophilic joints, hypertrophic scars, nonunion fractures, Osler-Weber syndrome, pyogenic granuloma, scleroderma, trachoma, and vascular adhesions.

[1132] Moreover, diseases, disorders, and/or conditions and/or states, which can be treated, prevented, and/or diagnosed with the the polynucleotides, polypeptides, agonists and/or antagonists include, but are not limited to, solid tumors, blood born



tumors such as leukemias, tumor metastasis, Kaposi's sarcoma, benign tumors, for example hemangiomas, acoustic neuromas, neurofibromas, trachomas, and pyogenic granulomas, rheumatoid arthritis, psoriasis, ocular angiogenic diseases, for example, diabetic retinopathy, retinopathy of prematurity, macular degeneration, corneal graft rejection, neovascular glaucoma, retrolental fibroplasia, rubeosis, retinoblastoma, and uveitis, delayed wound healing, endometriosis, vasculogenesis, granulations, hypertrophic scars (keloids), nonunion fractures, scleroderma, trachoma, vascular adhesions, myocardial angiogenesis, coronary collaterals, cerebral collaterals, arteriovenous malformations, ischemic limb angiogenesis, Osler-Webber Syndrome, plaque neovascularization, telangiectasia, hemophilic joints, angiofibroma fibromuscular dysplasia, wound granulation, Crohn's disease, atherosclerosis, birth control agent by preventing vascularization required for embryo implantation controlling menstruation, diseases that have angiogenesis as a pathologic consequence such as cat scratch disease (*Rochelina minalia quintosa*), ulcers (*Helicobacter pylori*), Bartonellosis and bacillary angiomatosis.

[1133] In one aspect of the birth control method, an amount of the compound sufficient to block embryo implantation is administered before or after intercourse and fertilization have occurred, thus providing an effective method of birth control, possibly a "morning after" method. Polynucleotides, polypeptides, agonists and/or antagonists may also be used in controlling menstruation or administered as either a peritoneal lavage fluid or for peritoneal implantation in the treatment of endometriosis.

[1134] Polynucleotides, polypeptides, agonists and/or antagonists of the present invention may be incorporated into surgical sutures in order to prevent stitch granulomas.

[1135] Polynucleotides, polypeptides, agonists and/or antagonists may be utilized in a wide variety of surgical procedures. For example, within one aspect of the present invention a composition (in the form of, for example, a spray or film) may be utilized to coat or spray an area prior to removal of a tumor, in order to isolate normal surrounding tissues from malignant tissue, and/or to prevent the spread of disease to surrounding tissues. Within other aspects of the present invention, compositions (e.g.,

in the form of a spray) may be delivered via endoscopic procedures in order to coat tumors, or inhibit angiogenesis in a desired locale. Within yet other aspects of the present invention, surgical meshes which have been coated with anti- angiogenic compositions of the present invention may be utilized in any procedure wherein a surgical mesh might be utilized. For example, within one embodiment of the invention a surgical mesh laden with an anti-angiogenic composition may be utilized during abdominal cancer resection surgery (e.g., subsequent to colon resection) in order to provide support to the structure, and to release an amount of the anti-angiogenic factor.

[1136] Within further aspects of the present invention, methods are provided for treating tumor excision sites, comprising administering a polynucleotide, polypeptide, agonist and/or agonist to the resection margins of a tumor subsequent to excision, such that the local recurrence of cancer and the formation of new blood vessels at the site is inhibited. Within one embodiment of the invention, the anti-angiogenic compound is administered directly to the tumor excision site (e.g., applied by swabbing, brushing or otherwise coating the resection margins of the tumor with the anti-angiogenic compound). Alternatively, the anti-angiogenic compounds may be incorporated into known surgical pastes prior to administration. Within particularly preferred embodiments of the invention, the anti-angiogenic compounds are applied after hepatic resections for malignancy, and after neurosurgical operations.

[1137] Within one aspect of the present invention, polynucleotides, polypeptides, agonists and/or agonists may be administered to the resection margin of a wide variety of tumors, including for example, breast, colon, brain and hepatic tumors. For example, within one embodiment of the invention, anti-angiogenic compounds may be administered to the site of a neurological tumor subsequent to excision, such that the formation of new blood vessels at the site are inhibited.

[1138] The polynucleotides, polypeptides, agonists and/or agonists of the present invention may also be administered along with other anti-angiogenic factors.

Representative examples of other anti-angiogenic factors include: Anti-Invasive Factor, retinoic acid and derivatives thereof, paclitaxel, Suramin, Tissue Inhibitor of Metalloproteinase-1, Tissue Inhibitor of Metalloproteinase-2, Plasminogen Activator

Inhibitor-1, Plasminogen Activator Inhibitor-2, and various forms of the lighter "d group" transition metals.

[1139] Lighter "d group" transition metals include, for example, vanadium, molybdenum, tungsten, titanium, niobium, and tantalum species. Such transition metal species may form transition metal complexes. Suitable complexes of the above-mentioned transition metal species include oxo transition metal complexes.

[1140] Representative examples of vanadium complexes include oxo vanadium complexes such as vanadate and vanadyl complexes. Suitable vanadate complexes include metavanadate and orthovanadate complexes such as, for example, ammonium metavanadate, sodium metavanadate, and sodium orthovanadate. Suitable vanadyl complexes include, for example, vanadyl acetylacetonate and vanadyl sulfate including vanadyl sulfate hydrates such as vanadyl sulfate mono- and trihydrates.

[1141] Representative examples of tungsten and molybdenum complexes also include oxo complexes. Suitable oxo tungsten complexes include tungstate and tungsten oxide complexes. Suitable tungstate complexes include ammonium tungstate, calcium tungstate, sodium tungstate dihydrate, and tungstic acid. Suitable tungsten oxides include tungsten (IV) oxide and tungsten (VI) oxide. Suitable oxo molybdenum complexes include molybdate, molybdenum oxide, and molybdenyl complexes. Suitable molybdate complexes include ammonium molybdate and its hydrates, sodium molybdate and its hydrates, and potassium molybdate and its hydrates. Suitable molybdenum oxides include molybdenum (VI) oxide, molybdenum (VI) oxide, and molybdic acid. Suitable molybdenyl complexes include, for example, molybdenyl acetylacetonate. Other suitable tungsten and molybdenum complexes include hydroxo derivatives derived from, for example, glycerol, tartaric acid, and sugars.

[1142] A wide variety of other anti-angiogenic factors may also be utilized within the context of the present invention. Representative examples include platelet factor 4; protamine sulphate; sulphated chitin derivatives (prepared from queen crab shells), (Murata et al., Cancer Res. 51:22-26, 1991); Sulphated Polysaccharide Peptidoglycan Complex (SP- PG) (the function of this compound may be enhanced by the presence of steroids such as estrogen, and tamoxifen citrate); Staurosporine; modulators of

matrix metabolism, including for example, proline analogs, cishydroxyproline, d,L-3,4-dehydroproline, Thiaproline, alpha,alpha-dipyridyl, aminopropionitrile fumarate; 4-propyl-5-(4-pyridinyl)-2(3H)-oxazolone; Methotrexate; Mitoxantrone; Heparin; Interferons; 2 Macroglobulin-serum; ChIMP-3 (Pavloff et al., J. Bio. Chem. 267:17321-17326, 1992); Chymostatin (Tomkinson et al., Biochem J. 286:475-480, 1992); Cyclodextrin Tetradasulfate; Eponemycin; Camptothecin; Fumagillin (Ingber et al., Nature 348:555-557, 1990); Gold Sodium Thiomalate ("GST"; Matsubara and Ziff, J. Clin. Invest. 79:1440-1446, 1987); anticollagenase-serum; alpha2-antiplasmin (Holmes et al., J. Biol. Chem. 262(4):1659-1664, 1987); Bisantrone (National Cancer Institute); Lobenzarit disodium (N-(2)-carboxyphenyl-4-chloroanthronilic acid disodium or "CCA"; Takeuchi et al., Agents Actions 36:312-316, 1992); Thalidomide; Angostatic steroid; AGM-1470; carboxyaminolimidazole; and metalloproteinase inhibitors such as BB94.

#### **[1143] Diseases at the Cellular Level**

[1144] Diseases associated with increased cell survival or the inhibition of apoptosis that could be treated, prevented, and/or diagnosed by the polynucleotides or polypeptides and/or antagonists or agonists of the invention, include cancers (such as follicular lymphomas, carcinomas with p53 mutations, and hormone-dependent tumors, including, but not limited to colon cancer, cardiac tumors, pancreatic cancer, melanoma, retinoblastoma, glioblastoma, lung cancer, intestinal cancer, testicular cancer, stomach cancer, neuroblastoma, myxoma, myoma, lymphoma, endothelioma, osteoblastoma, osteoclastoma, osteosarcoma, chondrosarcoma, adenoma, breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune diseases, disorders, and/or conditions (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and immune-related glomerulonephritis and rheumatoid arthritis) and viral infections (such as herpes viruses, pox viruses and adenoviruses), inflammation, graft v. host disease, acute graft rejection, and chronic graft rejection. In preferred embodiments, the polynucleotides or polypeptides, and/or agonists or antagonists of the invention are used to inhibit growth, progression, and/or metasis of cancers, in particular those listed above.

**[1145]** Additional diseases or conditions associated with increased cell survival that could be treated, prevented or diagnosed by the polynucleotides or polypeptides, or agonists or antagonists of the invention, include, but are not limited to, progression, and/or metastases of malignancies and related disorders such as leukemia (including acute leukemias (e.g., acute lymphocytic leukemia, acute myelocytic leukemia (including myeloblastic, promyelocytic, myelomonocytic, monocytic, and erythroleukemia)) and chronic leukemias (e.g., chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia)), polycythemia vera, lymphomas (e.g., Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, heavy chain disease, and solid tumors including, but not limited to, sarcomas and carcinomas such as fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilm's tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, menangioma, melanoma, neuroblastoma, and retinoblastoma.

**[1146]** Diseases associated with increased apoptosis that could be treated, prevented, and/or diagnosed by the polynucleotides or polypeptides, and/or agonists or antagonists of the invention, include AIDS; neurodegenerative diseases, disorders, and/or conditions (such as Alzheimer's disease, Parkinson's disease, Amyotrophic lateral sclerosis, Retinitis pigmentosa, Cerebellar degeneration and brain tumor or prior associated disease); autoimmune diseases, disorders, and/or conditions (such as, multiple sclerosis, Sjogren's syndrome, Hashimoto's thyroiditis, biliary cirrhosis, Behcet's disease, Crohn's disease, polymyositis, systemic lupus erythematosus and

immune-related glomerulonephritis and rheumatoid arthritis) myelodysplastic syndromes (such as aplastic anemia), graft v. host disease, ischemic injury (such as that caused by myocardial infarction, stroke and reperfusion injury), liver injury (e.g., hepatitis related liver injury, ischemia/reperfusion injury, cholestosis (bile duct injury) and liver cancer); toxin-induced liver disease (such as that caused by alcohol), septic shock, cachexia and anorexia.

**[1147] Wound Healing and Epithelial Cell Proliferation**

**[1148]** In accordance with yet a further aspect of the present invention, there is provided a process for utilizing the polynucleotides or polypeptides, and/or agonists or antagonists of the invention, for therapeutic purposes, for example, to stimulate epithelial cell proliferation and basal keratinocytes for the purpose of wound healing, and to stimulate hair follicle production and healing of dermal wounds.

Polynucleotides or polypeptides, as well as agonists or antagonists of the invention, may be clinically useful in stimulating wound healing including surgical wounds, excisional wounds, deep wounds involving damage of the dermis and epidermis, eye tissue wounds, dental tissue wounds, oral cavity wounds, diabetic ulcers, dermal ulcers, cubitus ulcers, arterial ulcers, venous stasis ulcers, burns resulting from heat exposure or chemicals, and other abnormal wound healing conditions such as uremia, malnutrition, vitamin deficiencies and complications associated with systemic treatment with steroids, radiation therapy and antineoplastic drugs and antimetabolites. Polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could be used to promote dermal reestablishment subsequent to dermal loss.

**[1149]** The polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could be used to increase the adherence of skin grafts to a wound bed and to stimulate re-epithelialization from the wound bed. The following are a non-exhaustive list of grafts that polynucleotides or polypeptides, agonists or antagonists of the invention, could be used to increase adherence to a wound bed: autografts, artificial skin, allografts, autodermic graft, autoepdermic grafts, avacular grafts, Blair-Brown grafts, bone graft, brephoplastic grafts, cutis graft, delayed graft, dermic graft,

epidermic graft, fascia graft, full thickness graft, heterologous graft, xenograft, homologous graft, hyperplastic graft, lamellar graft, mesh graft, mucosal graft, Ollier-Thiersch graft, omentum graft, patch graft, pedicle graft, penetrating graft, split skin graft, thick split graft. The polynucleotides or polypeptides, and/or agonists or antagonists of the invention, can be used to promote skin strength and to improve the appearance of aged skin.

[1150] It is believed that the polynucleotides or polypeptides, and/or agonists or antagonists of the invention, will also produce changes in hepatocyte proliferation, and epithelial cell proliferation in the lung, breast, pancreas, stomach, small intestine, and large intestine. The polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could promote proliferation of epithelial cells such as sebocytes, hair follicles, hepatocytes, type II pneumocytes, mucin-producing goblet cells, and other epithelial cells and their progenitors contained within the skin, lung, liver, and gastrointestinal tract. The polynucleotides or polypeptides, and/or agonists or antagonists of the invention, may promote proliferation of endothelial cells, keratinocytes, and basal keratinocytes.

[1151] The polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could also be used to reduce the side effects of gut toxicity that result from radiation, chemotherapy treatments or viral infections. The polynucleotides or polypeptides, and/or agonists or antagonists of the invention, may have a cytoprotective effect on the small intestine mucosa. The polynucleotides or polypeptides, and/or agonists or antagonists of the invention, may also stimulate healing of mucositis (mouth ulcers) that result from chemotherapy and viral infections.

[1152] The polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could further be used in full regeneration of skin in full and partial thickness skin defects, including burns, (i.e., repopulation of hair follicles, sweat glands, and sebaceous glands), treatment of other skin defects such as psoriasis. The polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could be used to treat epidermolysis bullosa, a defect in adherence of the epidermis to the underlying dermis which results in frequent, open and painful blisters by accelerating

reepithelialization of these lesions. The polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could also be used to treat gastric and duodenal ulcers and help heal by scar formation of the mucosal lining and regeneration of glandular mucosa and duodenal mucosal lining more rapidly. Inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis, are diseases which result in destruction of the mucosal surface of the small or large intestine, respectively. Thus, the polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could be used to promote the resurfacing of the mucosal surface to aid more rapid healing and to prevent progression of inflammatory bowel disease. Treatment with the polynucleotides or polypeptides, and/or agonists or antagonists of the invention, is expected to have a significant effect on the production of mucus throughout the gastrointestinal tract and could be used to protect the intestinal mucosa from injurious substances that are ingested or following surgery. The polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could be used to treat diseases associated with the under expression of the polynucleotides of the invention.

[1153] Moreover, the polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could be used to prevent and heal damage to the lungs due to various pathological states. A growth factor such as the polynucleotides or polypeptides, and/or agonists or antagonists of the invention, which could stimulate proliferation and differentiation and promote the repair of alveoli and bronchiolar epithelium to prevent or treat acute or chronic lung damage. For example, emphysema, which results in the progressive loss of alveoli, and inhalation injuries, i.e., resulting from smoke inhalation and burns, that cause necrosis of the bronchiolar epithelium and alveoli could be effectively treated, prevented, and/or diagnosed using the polynucleotides or polypeptides, and/or agonists or antagonists of the invention. Also, the polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could be used to stimulate the proliferation of and differentiation of type II pneumocytes, which may help treat or prevent disease such as hyaline membrane diseases, such as infant respiratory distress syndrome and bronchopulmonary dysplasia, in premature infants.



[1154] The polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could stimulate the proliferation and differentiation of hepatocytes and, thus, could be used to alleviate or treat liver diseases and pathologies such as fulminant liver failure caused by cirrhosis, liver damage caused by viral hepatitis and toxic substances (i.e., acetaminophen, carbon tetrachloride and other hepatotoxins known in the art).

[1155] In addition, the polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could be used to treat or prevent the onset of diabetes mellitus. In patients with newly diagnosed Types I and II diabetes, where some islet cell function remains, the polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could be used to maintain the islet function so as to alleviate, delay or prevent permanent manifestation of the disease. Also, the polynucleotides or polypeptides, and/or agonists or antagonists of the invention, could be used as an auxiliary in islet cell transplantation to improve or promote islet cell function.

#### **[1156] Neurological Diseases**

[1157] Nervous system diseases, disorders, and/or conditions, which can be treated, prevented, and/or diagnosed with the compositions of the invention (e.g., polypeptides, polynucleotides, and/or agonists or antagonists), include, but are not limited to, nervous system injuries, and diseases, disorders, and/or conditions which result in either a disconnection of axons, a diminution or degeneration of neurons, or demyelination. Nervous system lesions which may be treated, prevented, and/or diagnosed in a patient (including human and non-human mammalian patients) according to the invention, include but are not limited to, the following lesions of either the central (including spinal cord, brain) or peripheral nervous systems: (1) ischemic lesions, in which a lack of oxygen in a portion of the nervous system results in neuronal injury or death, including cerebral infarction or ischemia, or spinal cord infarction or ischemia; (2) traumatic lesions, including lesions caused by physical injury or associated with surgery, for example, lesions which sever a portion of the nervous system, or compression injuries; (3) malignant lesions, in which a portion of

the nervous system is destroyed or injured by malignant tissue which is either a nervous system associated malignancy or a malignancy derived from non-nervous system tissue; (4) infectious lesions, in which a portion of the nervous system is destroyed or injured as a result of infection, for example, by an abscess or associated with infection by human immunodeficiency virus, herpes zoster, or herpes simplex virus or with Lyme disease, tuberculosis, syphilis; (5) degenerative lesions, in which a portion of the nervous system is destroyed or injured as a result of a degenerative process including but not limited to degeneration associated with Parkinson's disease, Alzheimer's disease, Huntington's chorea, or amyotrophic lateral sclerosis (ALS); (6) lesions associated with nutritional diseases, disorders, and/or conditions, in which a portion of the nervous system is destroyed or injured by a nutritional disorder or disorder of metabolism including but not limited to, vitamin B12 deficiency, folic acid deficiency, Wernicke disease, tobacco-alcohol amblyopia, Marchiafava-Bignami disease (primary degeneration of the corpus callosum), and alcoholic cerebellar degeneration; (7) neurological lesions associated with systemic diseases including, but not limited to, diabetes (diabetic neuropathy, Bell's palsy), systemic lupus erythematosus, carcinoma, or sarcoidosis; (8) lesions caused by toxic substances including alcohol, lead, or particular neurotoxins; and (9) demyelinated lesions in which a portion of the nervous system is destroyed or injured by a demyelinating disease including, but not limited to, multiple sclerosis, human immunodeficiency virus-associated myelopathy, transverse myelopathy or various etiologies, progressive multifocal leukoencephalopathy, and central pontine myelinolysis.

[1158] In a preferred embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to protect neural cells from the damaging effects of cerebral hypoxia. According to this embodiment, the compositions of the invention are used to treat, prevent, and/or diagnose neural cell injury associated with cerebral hypoxia. In one aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat, prevent, and/or diagnose neural cell injury associated with cerebral ischemia. In another aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat, prevent, and/or diagnose neural cell

injury associated with cerebral infarction. In another aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat, prevent, and/or diagnose or prevent neural cell injury associated with a stroke. In a further aspect of this embodiment, the polypeptides, polynucleotides, or agonists or antagonists of the invention are used to treat, prevent, and/or diagnose neural cell injury associated with a heart attack.

[1159] The compositions of the invention which are useful for treating or preventing a nervous system disorder may be selected by testing for biological activity in promoting the survival or differentiation of neurons. For example, and not by way of limitation, compositions of the invention which elicit any of the following effects may be useful according to the invention: (1) increased survival time of neurons in culture; (2) increased sprouting of neurons in culture or *in vivo*; (3) increased production of a neuron-associated molecule in culture or *in vivo*, e.g., choline acetyltransferase or acetylcholinesterase with respect to motor neurons; or (4) decreased symptoms of neuron dysfunction *in vivo*. Such effects may be measured by any method known in the art. In preferred, non-limiting embodiments, increased survival of neurons may routinely be measured using a method set forth herein or otherwise known in the art, such as, for example, the method set forth in Arakawa et al. (J. Neurosci. 10:3507-3515 (1990)); increased sprouting of neurons may be detected by methods known in the art, such as, for example, the methods set forth in Pestronk et al. (Exp. Neurol. 70:65-82 (1980)) or Brown et al. (Ann. Rev. Neurosci. 4:17-42 (1981)); increased production of neuron-associated molecules may be measured by bioassay, enzymatic assay, antibody binding, Northern blot assay, etc., using techniques known in the art and depending on the molecule to be measured; and motor neuron dysfunction may be measured by assessing the physical manifestation of motor neuron disorder, e.g., weakness, motor neuron conduction velocity, or functional disability.

[1160] In specific embodiments, motor neuron diseases, disorders, and/or conditions that may be treated, prevented, and/or diagnosed according to the invention include, but are not limited to, diseases, disorders, and/or conditions such as infarction, infection, exposure to toxin, trauma, surgical damage, degenerative disease or

malignancy that may affect motor neurons as well as other components of the nervous system, as well as diseases, disorders, and/or conditions that selectively affect neurons such as amyotrophic lateral sclerosis, and including, but not limited to, progressive spinal muscular atrophy, progressive bulbar palsy, primary lateral sclerosis, infantile and juvenile muscular atrophy, progressive bulbar paralysis of childhood (Fazio-Londe syndrome), poliomyelitis and the post polio syndrome, and Hereditary Motorsensory Neuropathy (Charcot-Marie-Tooth Disease).

**[1161] Infectious Disease**

**[1162]** A polypeptide or polynucleotide and/or agonist or antagonist of the present invention can be used to treat, prevent, and/or diagnose infectious agents. For example, by increasing the immune response, particularly increasing the proliferation and differentiation of B and/or T cells, infectious diseases may be treated, prevented, and/or diagnosed. The immune response may be increased by either enhancing an existing immune response, or by initiating a new immune response. Alternatively, polypeptide or polynucleotide and/or agonist or antagonist of the present invention may also directly inhibit the infectious agent, without necessarily eliciting an immune response.

**[1163]** Viruses are one example of an infectious agent that can cause disease or symptoms that can be treated, prevented, and/or diagnosed by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention. Examples of viruses, include, but are not limited to Examples of viruses, include, but are not limited to the following DNA and RNA viruses and viral families: Arbovirus, Adenoviridae, Arenaviridae, Arterivirus, Birnaviridae, Bunyaviridae, Caliciviridae, Circoviridae, Coronaviridae, Dengue, EBV, HIV, Flaviviridae, Hepadnaviridae (Hepatitis), Herpesviridae (such as, Cytomegalovirus, Herpes Simplex, Herpes Zoster), Mononegavirus (e.g., Paramyxoviridae, Morbillivirus, Rhabdoviridae), Orthomyxoviridae (e.g., Influenza A, Influenza B, and parainfluenza), Papilloma virus, Papovaviridae, Parvoviridae, Picornaviridae, Poxviridae (such as Smallpox or Vaccinia), Reoviridae (e.g., Rotavirus), Retroviridae (HTLV-I, HTLV-II, Lentivirus), and Togaviridae (e.g., Rubivirus). Viruses falling within these families can cause a

variety of diseases or symptoms, including, but not limited to: arthritis, bronchiollitis, respiratory syncytial virus, encephalitis, eye infections (e.g., conjunctivitis, keratitis), chronic fatigue syndrome, hepatitis (A, B, C, E, Chronic Active, Delta), Japanese B encephalitis, Junin, Chikungunya, Rift Valley fever, yellow fever, meningitis, opportunistic infections (e.g., AIDS), pneumonia, Burkitt's Lymphoma, chickenpox, hemorrhagic fever, Measles, Mumps, Parainfluenza, Rabies, the common cold, Polio, leukemia, Rubella, sexually transmitted diseases, skin diseases (e.g., Kaposi's, warts), and viremia. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat, prevent, and/or diagnose any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat, prevent, and/or diagnose: meningitis, Dengue, EBV, and/or hepatitis (e.g., hepatitis B). In an additional specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat patients nonresponsive to one or more other commercially available hepatitis vaccines. In a further specific embodiment polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat, prevent, and/or diagnose AIDS.

[1164] Similarly, bacterial or fungal agents that can cause disease or symptoms and that can be treated, prevented, and/or diagnosed by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, include, but not limited to, the following Gram-Negative and Gram-positive bacteria and bacterial families and fungi: Actinomycetales (e.g., Corynebacterium, Mycobacterium, Norcardia), Cryptococcus neoformans, Aspergillosis, Bacillaceae (e.g., Anthrax, Clostridium), Bacteroidaceae, Blastomycosis, Bordetella, Borrelia (e.g., Borrelia burgdorferi), Brucellosis, Candidiasis, Campylobacter, Coccidioidomycosis, Cryptococcosis, Dermatocycoses, E. coli (e.g., Enterotoxigenic E. coli and Enterohemorrhagic E. coli), Enterobacteriaceae (Klebsiella, Salmonella (e.g., Salmonella typhi, and Salmonella paratyphi), Serratia, Yersinia), Erysipelothrix, Helicobacter, Legionellosis, Leptospirosis, Listeria, Mycoplasmatales, Mycobacterium leprae, Vibrio cholerae, Neisseriaceae (e.g., Acinetobacter, Gonorrhea, Meningococcal), Meisseria meningitidis, Pasteurellacea Infections (e.g.,

Actinobacillus, Haemophilus (e.g., Haemophilus influenza type B), Pasteurella, Pseudomonas, Rickettsiaceae, Chlamydiaceae, Syphilis, Shigella spp., Staphylococcal, Meningococcal, Pneumococcal and Streptococcal (e.g., Streptococcus pneumoniae and Group B Streptococcus). These bacterial or fungal families can cause the following diseases or symptoms, including, but not limited to: bacteremia, endocarditis, eye infections (conjunctivitis, tuberculosis, uveitis), gingivitis, opportunistic infections (e.g., AIDS related infections), paronychia, prosthesis-related infections, Reiter's Disease, respiratory tract infections, such as Whooping Cough or Empyema, sepsis, Lyme Disease, Cat-Scratch Disease, Dysentery, Paratyphoid Fever, food poisoning, Typhoid, pneumonia, Gonorrhea, meningitis (e.g., meningitis types A and B), Chlamydia, Syphilis, Diphtheria, Leprosy, Paratuberculosis, Tuberculosis, Lupus, Botulism, gangrene, tetanus, impetigo, Rheumatic Fever, Scarlet Fever, sexually transmitted diseases, skin diseases (e.g., cellulitis, dermatocycoses), toxemia, urinary tract infections, wound infections. Polynucleotides or polypeptides, agonists or antagonists of the invention, can be used to treat, prevent, and/or diagnose any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, agonists or antagonists of the invention are used to treat, prevent, and/or diagnose: tetanus, Diphtheria, botulism, and/or meningitis type B.

[1165] Moreover, parasitic agents causing disease or symptoms that can be treated, prevented, and/or diagnosed by a polynucleotide or polypeptide and/or agonist or antagonist of the present invention include, but not limited to, the following families or class: Amebiasis, Babesiosis, Coccidiosis, Cryptosporidiosis, Dientamoebiasis, Dourine, Ectoparasitic, Giardiasis, Helminthiasis, Leishmaniasis, Theileriasis, Toxoplasmosis, Trypanosomiasis, and Trichomonas and Sporozoans (e.g., Plasmodium virax, Plasmodium falciparum, Plasmodium malariae and Plasmodium ovale). These parasites can cause a variety of diseases or symptoms, including, but not limited to: Scabies, Trombiculiasis, eye infections, intestinal disease (e.g., dysentery, giardiasis), liver disease, lung disease, opportunistic infections (e.g., AIDS related), malaria, pregnancy complications, and toxoplasmosis. polynucleotides or polypeptides, or agonists or antagonists of the invention, can be used to treat, prevent,

and/or diagnose any of these symptoms or diseases. In specific embodiments, polynucleotides, polypeptides, or agonists or antagonists of the invention are used to treat, prevent, and/or diagnose malaria.

**[1166]** Preferably, treatment or prevention using a polypeptide or polynucleotide and/or agonist or antagonist of the present invention could either be by administering an effective amount of a polypeptide to the patient, or by removing cells from the patient, supplying the cells with a polynucleotide of the present invention, and returning the engineered cells to the patient (*ex vivo* therapy). Moreover, the polypeptide or polynucleotide of the present invention can be used as an antigen in a vaccine to raise an immune response against infectious disease.

**[1167] Regeneration**

**[1168]** A polynucleotide or polypeptide and/or agonist or antagonist of the present invention can be used to differentiate, proliferate, and attract cells, leading to the regeneration of tissues. (See, Science 276:59-87 (1997).) The regeneration of tissues could be used to repair, replace, or protect tissue damaged by congenital defects, trauma (wounds, burns, incisions, or ulcers), age, disease (e.g. osteoporosis, osteoarthritis, periodontal disease, liver failure), surgery, including cosmetic plastic surgery, fibrosis, reperfusion injury, or systemic cytokine damage.

**[1169]** Tissues that could be regenerated using the present invention include organs (e.g., pancreas, liver, intestine, kidney, skin, endothelium), muscle (smooth, skeletal or cardiac), vasculature (including vascular and lymphatics), nervous, hematopoietic, and skeletal (bone, cartilage, tendon, and ligament) tissue. Preferably, regeneration occurs without or decreased scarring. Regeneration also may include angiogenesis.

**[1170]** Moreover, a polynucleotide or polypeptide and/or agonist or antagonist of the present invention may increase regeneration of tissues difficult to heal. For example, increased tendon/ligament regeneration would quicken recovery time after damage.

A polynucleotide or polypeptide and/or agonist or antagonist of the present invention could also be used prophylactically in an effort to avoid damage. Specific diseases that could be treated, prevented, and/or diagnosed include of tendinitis, carpal tunnel syndrome, and other tendon or ligament defects. A further example of tissue

regeneration of non-healing wounds includes pressure ulcers, ulcers associated with vascular insufficiency, surgical, and traumatic wounds.

[1171] Similarly, nerve and brain tissue could also be regenerated by using a polynucleotide or polypeptide and/or agonist or antagonist of the present invention to proliferate and differentiate nerve cells. Diseases that could be treated, prevented, and/or diagnosed using this method include central and peripheral nervous system diseases, neuropathies, or mechanical and traumatic diseases, disorders, and/or conditions (e.g., spinal cord disorders, head trauma, cerebrovascular disease, and stroke). Specifically, diseases associated with peripheral nerve injuries, peripheral neuropathy (e.g., resulting from chemotherapy or other medical therapies), localized neuropathies, and central nervous system diseases (e.g., Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Shy-Drager syndrome), could all be treated, prevented, and/or diagnosed using the polynucleotide or polypeptide and/or agonist or antagonist of the present invention.

**[1172] Chemotaxis**

[1173] A polynucleotide or polypeptide and/or agonist or antagonist of the present invention may have chemotaxis activity. A chemotactic molecule attracts or mobilizes cells (e.g., monocytes, fibroblasts, neutrophils, T-cells, mast cells, eosinophils, epithelial and/or endothelial cells) to a particular site in the body, such as inflammation, infection, or site of hyperproliferation. The mobilized cells can then fight off and/or heal the particular trauma or abnormality.

[1174] A polynucleotide or polypeptide and/or agonist or antagonist of the present invention may increase chemotactic activity of particular cells. These chemotactic molecules can then be used to treat, prevent, and/or diagnose inflammation, infection, hyperproliferative diseases, disorders, and/or conditions, or any immune system disorder by increasing the number of cells targeted to a particular location in the body. For example, chemotactic molecules can be used to treat, prevent, and/or diagnose wounds and other trauma to tissues by attracting immune cells to the injured location. Chemotactic molecules of the present invention can also attract fibroblasts, which can be used to treat, prevent, and/or diagnose wounds.



[1175] It is also contemplated that a polynucleotide or polypeptide and/or agonist or antagonist of the present invention may inhibit chemotactic activity. These molecules could also be used to treat, prevent, and/or diagnose diseases, disorders, and/or conditions. Thus, a polynucleotide or polypeptide and/or agonist or antagonist of the present invention could be used as an inhibitor of chemotaxis.

**[1176] Binding Activity**

[1177] A polypeptide of the present invention may be used to screen for molecules that bind to the polypeptide or for molecules to which the polypeptide binds. The binding of the polypeptide and the molecule may activate (agonist), increase, inhibit (antagonist), or decrease activity of the polypeptide or the molecule bound. Examples of such molecules include antibodies, oligonucleotides, proteins (e.g., receptors), or small molecules.

[1178] Preferably, the molecule is closely related to the natural ligand of the polypeptide, e.g., a fragment of the ligand, or a natural substrate, a ligand, a structural or functional mimetic. (See, Coligan et al., Current Protocols in Immunology 1(2):Chapter 5 (1991).) Similarly, the molecule can be closely related to the natural receptor to which the polypeptide binds, or at least, a fragment of the receptor capable of being bound by the polypeptide (e.g., active site). In either case, the molecule can be rationally designed using known techniques.

[1179] Preferably, the screening for these molecules involves producing appropriate cells which express the polypeptide, either as a secreted protein or on the cell membrane. Preferred cells include cells from mammals, yeast, *Drosophila*, or *E. coli*. Cells expressing the polypeptide (or cell membrane containing the expressed polypeptide) are then preferably contacted with a test compound potentially containing the molecule to observe binding, stimulation, or inhibition of activity of either the polypeptide or the molecule.

[1180] The assay may simply test binding of a candidate compound to the polypeptide, wherein binding is detected by a label, or in an assay involving

competition with a labeled competitor. Further, the assay may test whether the candidate compound results in a signal generated by binding to the polypeptide.

[1181] Alternatively, the assay can be carried out using cell-free preparations, polypeptide/molecule affixed to a solid support, chemical libraries, or natural product mixtures. The assay may also simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide, measuring polypeptide/molecule activity or binding, and comparing the polypeptide/molecule activity or binding to a standard.

[1182] Preferably, an ELISA assay can measure polypeptide level or activity in a sample (e.g., biological sample) using a monoclonal or polyclonal antibody. The antibody can measure polypeptide level or activity by either binding, directly or indirectly, to the polypeptide or by competing with the polypeptide for a substrate.

[1183] Additionally, the receptor to which a polypeptide of the invention binds can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting (Coligan, et al., *Current Protocols in Immun.*, 1(2), Chapter 5, (1991)). For example, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the polypeptides, for example, NIH3T3 cells which are known to contain multiple receptors for the FGF family proteins, and SC-3 cells, and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the polypeptides. Transfected cells which are grown on glass slides are exposed to the polypeptide of the present invention, after they have been labelled. The polypeptides can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase.

[1184] Following fixation and incubation, the slides are subjected to autoradiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an iterative sub-pooling and re-screening process, eventually yielding a single clones that encodes the putative receptor.

[1185] As an alternative approach for receptor identification, the labeled polypeptides can be photoaffinity linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE analysis and

exposed to X-ray film. The labeled complex containing the receptors of the polypeptides can be excised, resolved into peptide fragments, and subjected to protein microsequencing. The amino acid sequence obtained from microsequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the genes encoding the putative receptors.

[1186] Moreover, the techniques of gene-shuffling, motif-shuffling, exon-shuffling, and/or codon-shuffling (collectively referred to as "DNA shuffling") may be employed to modulate the activities of polypeptides of the invention thereby effectively generating agonists and antagonists of polypeptides of the invention. See generally, U.S. Patent Nos. 5,605,793, 5,811,238, 5,830,721, 5,834,252, and 5,837,458, and Patten, P. A., et al., *Curr. Opin. Biotechnol.* 8:724-33 (1997); Harayama, S. *Trends Biotechnol.* 16(2):76-82 (1998); Hansson, L. O., et al., *J. Mol. Biol.* 287:265-76 (1999); and Lorenzo, M. M. and Blasco, R. *Biotechniques* 24(2):308-13 (1998) (each of these patents and publications are hereby incorporated by reference). In one embodiment, alteration of polynucleotides and corresponding polypeptides of the invention may be achieved by DNA shuffling. DNA shuffling involves the assembly of two or more DNA segments into a desired polynucleotide sequence of the invention molecule by homologous, or site-specific, recombination. In another embodiment, polynucleotides and corresponding polypeptides of the invention may be altered by being subjected to random mutagenesis by error-prone PCR, random nucleotide insertion or other methods prior to recombination. In another embodiment, one or more components, motifs, sections, parts, domains, fragments, etc., of the polypeptides of the invention may be recombined with one or more components, motifs, sections, parts, domains, fragments, etc. of one or more heterologous molecules. In preferred embodiments, the heterologous molecules are family members. In further preferred embodiments, the heterologous molecule is a growth factor such as, for example, platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I), transforming growth factor (TGF)-alpha, epidermal growth factor (EGF), fibroblast growth factor (FGF), TGF-beta, bone morphogenetic protein (BMP)-2, BMP-4, BMP-5, BMP-6, BMP-7, activins A and B, decapentaplegic(dpp), 60A, OP-2, dorsalin, growth differentiation factors (GDFs),

nodal, MIS, inhibin-alpha, TGF-beta1, TGF-beta2, TGF-beta3, TGF-beta5, and glial-derived neurotrophic factor (GDNF).

[1187] Other preferred fragments are biologically active fragments of the polypeptides of the invention. Biologically active fragments are those exhibiting activity similar, but not necessarily identical, to an activity of the polypeptide. The biological activity of the fragments may include an improved desired activity, or a decreased undesirable activity.

[1188] Additionally, this invention provides a method of screening compounds to identify those which modulate the action of the polypeptide of the present invention. An example of such an assay comprises combining a mammalian fibroblast cell, a the polypeptide of the present invention, the compound to be screened and 3[H] thymidine under cell culture conditions where the fibroblast cell would normally proliferate. A control assay may be performed in the absence of the compound to be screened and compared to the amount of fibroblast proliferation in the presence of the compound to determine if the compound stimulates proliferation by determining the uptake of 3[H] thymidine in each case. The amount of fibroblast cell proliferation is measured by liquid scintillation chromatography which measures the incorporation of 3[H] thymidine. Both agonist and antagonist compounds may be identified by this procedure.

[1189] In another method, a mammalian cell or membrane preparation expressing a receptor for a polypeptide of the present invention is incubated with a labeled polypeptide of the present invention in the presence of the compound. The ability of the compound to enhance or block this interaction could then be measured. Alternatively, the response of a known second messenger system following interaction of a compound to be screened and the receptor is measured and the ability of the compound to bind to the receptor and elicit a second messenger response is measured to determine if the compound is a potential agonist or antagonist. Such second messenger systems include but are not limited to, cAMP guanylate cyclase, ion channels or phosphoinositide hydrolysis.

[1190] All of these above assays can be used as diagnostic or prognostic markers. The molecules discovered using these assays can be used to treat, prevent, and/or

diagnose disease or to bring about a particular result in a patient (e.g., blood vessel growth) by activating or inhibiting the polypeptide/molecule. Moreover, the assays can discover agents which may inhibit or enhance the production of the polypeptides of the invention from suitably manipulated cells or tissues. Therefore, the invention includes a method of identifying compounds which bind to the polypeptides of the invention comprising the steps of: (a) incubating a candidate binding compound with the polypeptide; and (b) determining if binding has occurred. Moreover, the invention includes a method of identifying agonists/antagonists comprising the steps of: (a) incubating a candidate compound with the polypeptide, (b) assaying a biological activity, and (b) determining if a biological activity of the polypeptide has been altered.

[1191] Also, one could identify molecules bind a polypeptide of the invention experimentally by using the beta-pleated sheet regions contained in the polypeptide sequence of the protein. Accordingly, specific embodiments of the invention are directed to polynucleotides encoding polypeptides which comprise, or alternatively consist of, the amino acid sequence of each beta pleated sheet regions in a disclosed polypeptide sequence. Additional embodiments of the invention are directed to polynucleotides encoding polypeptides which comprise, or alternatively consist of, any combination or all of contained in the polypeptide sequences of the invention. Additional preferred embodiments of the invention are directed to polypeptides which comprise, or alternatively consist of, the amino acid sequence of each of the beta pleated sheet regions in one of the polypeptide sequences of the invention. Additional embodiments of the invention are directed to polypeptides which comprise, or alternatively consist of, any combination or all of the beta pleated sheet regions in one of the polypeptide sequences of the invention.

**[1192] Targeted Delivery**

[1193] In another embodiment, the invention provides a method of delivering compositions to targeted cells expressing a receptor for a polypeptide of the invention, or cells expressing a cell bound form of a polypeptide of the invention.

[1194] As discussed herein, polypeptides or antibodies of the invention may be

associated with heterologous polypeptides, heterologous nucleic acids, toxins, or prodrugs via hydrophobic, hydrophilic, ionic and/or covalent interactions. In one embodiment, the invention provides a method for the specific delivery of compositions of the invention to cells by administering polypeptides of the invention (including antibodies) that are associated with heterologous polypeptides or nucleic acids. In one example, the invention provides a method for delivering a therapeutic protein into the targeted cell. In another example, the invention provides a method for delivering a single stranded nucleic acid (e.g., antisense or ribozymes) or double stranded nucleic acid (e.g., DNA that can integrate into the cell's genome or replicate episomally and that can be transcribed) into the targeted cell.

[1195] In another embodiment, the invention provides a method for the specific destruction of cells (e.g., the destruction of tumor cells) by administering polypeptides of the invention (e.g., polypeptides of the invention or antibodies of the invention) in association with toxins or cytotoxic prodrugs.

[1196] By "toxin" is meant compounds that bind and activate endogenous cytotoxic effector systems, radioisotopes, holotoxins, modified toxins, catalytic subunits of toxins, or any molecules or enzymes not normally present in or on the surface of a cell that under defined conditions cause the cell's death. Toxins that may be used according to the methods of the invention include, but are not limited to, radioisotopes known in the art, compounds such as, for example, antibodies (or complement fixing containing portions thereof) that bind an inherent or induced endogenous cytotoxic effector system, thymidine kinase, endonuclease, RNase, alpha toxin, ricin, abrin, *Pseudomonas* exotoxin A, diphtheria toxin, saporin, momordin, gelonin, pokeweed antiviral protein, alpha-sarcin and cholera toxin. By "cytotoxic prodrug" is meant a non-toxic compound that is converted by an enzyme, normally present in the cell, into a cytotoxic compound. Cytotoxic prodrugs that may be used according to the methods of the invention include, but are not limited to, glutamyl derivatives of benzoic acid mustard alkylating agent, phosphate derivatives of etoposide or mitomycin C, cytosine arabinoside, daunorubisin, and phenoxyacetamide derivatives of doxorubicin.

**[1197] Drug Screening**

**[1198]** Further contemplated is the use of the polypeptides of the present invention, or the polynucleotides encoding these polypeptides, to screen for molecules which modify the activities of the polypeptides of the present invention. Such a method would include contacting the polypeptide of the present invention with a selected compound(s) suspected of having antagonist or agonist activity, and assaying the activity of these polypeptides following binding.

**[1199]** This invention is particularly useful for screening therapeutic compounds by using the polypeptides of the present invention, or binding fragments thereof, in any of a variety of drug screening techniques. The polypeptide or fragment employed in such a test may be affixed to a solid support, expressed on a cell surface, free in solution, or located intracellularly. One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. One may measure, for example, the formulation of complexes between the agent being tested and a polypeptide of the present invention.

**[1200]** Thus, the present invention provides methods of screening for drugs or any other agents which affect activities mediated by the polypeptides of the present invention. These methods comprise contacting such an agent with a polypeptide of the present invention or a fragment thereof and assaying for the presence of a complex between the agent and the polypeptide or a fragment thereof, by methods well known in the art. In such a competitive binding assay, the agents to screen are typically labeled. Following incubation, free agent is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of a particular agent to bind to the polypeptides of the present invention.

**[1201]** Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to the polypeptides of the present invention, and is described in great detail in European Patent Application 84/03564, published on September 13, 1984, which is incorporated herein by reference herein.

Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. The peptide test compounds are reacted with polypeptides of the present invention and washed. Bound polypeptides are then detected by methods well known in the art. Purified polypeptides are coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies may be used to capture the peptide and immobilize it on the solid support.

[1202] This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding polypeptides of the present invention specifically compete with a test compound for binding to the polypeptides or fragments thereof. In this manner, the antibodies are used to detect the presence of any peptide which shares one or more antigenic epitopes with a polypeptide of the invention.

**[1203] Antisense And Ribozyme (Antagonists)**

[1204] In specific embodiments, antagonists according to the present invention are nucleic acids corresponding to the sequences contained in SEQ ID NO:X, or the complementary strand thereof, and/or to nucleotide sequences contained a deposited clone. In one embodiment, antisense sequence is generated internally by the organism, in another embodiment, the antisense sequence is separately administered (see, for example, O'Connor, Neurochem., 56:560 (1991). Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988).

Antisense technology can be used to control gene expression through antisense DNA or RNA, or through triple-helix formation. Antisense techniques are discussed for example, in Okano, Neurochem., 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression, CRC Press, Boca Raton, FL (1988). Triple helix formation is discussed in, for instance, Lee et al., Nucleic Acids Research, 6:3073 (1979); Cooney et al., Science, 241:456 (1988); and Dervan et al., Science, 251:1300 (1991). The methods are based on binding of a polynucleotide to a complementary DNA or RNA.



[1205] For example, the use of c-myc and c-myb antisense RNA constructs to inhibit the growth of the non-lymphocytic leukemia cell line HL-60 and other cell lines was previously described. (Wickstrom et al. (1988); Anfossi et al. (1989)). These experiments were performed in vitro by incubating cells with the oligoribonucleotide. A similar procedure for in vivo use is described in WO 91/15580. Briefly, a pair of oligonucleotides for a given antisense RNA is produced as follows: A sequence complimentary to the first 15 bases of the open reading frame is flanked by an EcoRI site on the 5' end and a HindIII site on the 3' end. Next, the pair of oligonucleotides is heated at 90°C for one minute and then annealed in 2X ligation buffer (20mM TRIS HCl pH 7.5, 10mM MgCl<sub>2</sub>, 10mM dithiothreitol (DTT) and 0.2 mM ATP) and then ligated to the EcoRI/Hind III site of the retroviral vector PMV7 (WO 91/15580).

[1206] For example, the 5' coding portion of a polynucleotide that encodes the mature polypeptide of the present invention may be used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription thereby preventing transcription and the production of the receptor. The antisense RNA oligonucleotide hybridizes to the mRNA in vivo and blocks translation of the mRNA molecule into receptor polypeptide.

[1207] In one embodiment, the antisense nucleic acid of the invention is produced intracellularly by transcription from an exogenous sequence. For example, a vector or a portion thereof, is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the antisense nucleic acid of the invention. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art, used for replication and expression in vertebrate cells. Expression of the sequence encoding a polypeptide of the invention, or fragments thereof, can be by any promoter known in the art to act in vertebrate, preferably human cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, Nature, 29:304-310 (1981), the promoter

contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., Cell, 22:787-797 (1980), the herpes thymidine promoter (Wagner et al., Proc. Natl. Acad. Sci. U.S.A., 78:1441-1445 (1981), the regulatory sequences of the metallothionein gene (Brinster et al., Nature, 296:39-42 (1982)), etc.

[1208] The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a gene of interest. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double stranded antisense nucleic acids of the invention, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the larger the hybridizing nucleic acid, the more base mismatches with a RNA sequence of the invention it may contain and still form a stable duplex (or triplex as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

[1209] Oligonucleotides that are complementary to the 5' end of the message, *e.g.*, the 5' untranslated sequence up to and including the AUG initiation codon, should work most efficiently at inhibiting translation. However, sequences complementary to the 3' untranslated sequences of mRNAs have been shown to be effective at inhibiting translation of mRNAs as well. See generally, Wagner, R., *Nature*, 372:333-335 (1994). Thus, oligonucleotides complementary to either the 5' - or 3' - non-translated, non-coding regions of a polynucleotide sequence of the invention could be used in an antisense approach to inhibit translation of endogenous mRNA. Oligonucleotides complementary to the 5' untranslated region of the mRNA should include the complement of the AUG start codon. Antisense oligonucleotides complementary to mRNA coding regions are less efficient inhibitors of translation but could be used in accordance with the invention. Whether designed to hybridize to the 5' -, 3' - or coding region of mRNA, antisense nucleic acids should be at least six nucleotides in length, and are preferably oligonucleotides ranging from 6 to about 50

nucleotides in length. In specific aspects the oligonucleotide is at least 10 nucleotides, at least 17 nucleotides, at least 25 nucleotides or at least 50 nucleotides.

[1210] The polynucleotides of the invention can be DNA or RNA or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotide may include other appended groups such as peptides (e.g., for targeting host cell receptors in vivo), or agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., *Proc. Natl. Acad. Sci. U.S.A.* 86:6553-6556 (1989); Lemaitre et al., *Proc. Natl. Acad. Sci.*, 84:648-652 (1987); PCT Publication NO: WO88/09810, published December 15, 1988) or the blood-brain barrier (see, e.g., PCT Publication NO: WO89/10134, published April 25, 1988), hybridization-triggered cleavage agents. (See, e.g., Krol et al., *BioTechniques*, 6:958-976 (1988)) or intercalating agents. (See, e.g., Zon, *Pharm. Res.*, 5:539-549 (1988)). To this end, the oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

[1211] The antisense oligonucleotide may comprise at least one modified base moiety which is selected from the group including, but not limited to, 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xantine, 4-acetylcytosine, 5-(carboxyhydroxymethyl) uracil, 5-carboxymethylaminomethyl-2-thiouridine, 5-carboxymethylaminomethyluracil, dihydrouracil, beta-D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil, beta-D-mannosylqueosine, 5'-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v),

5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

[1212] The antisense oligonucleotide may also comprise at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

[1213] In yet another embodiment, the antisense oligonucleotide comprises at least one modified phosphate backbone selected from the group including, but not limited to, a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal or analog thereof.

[1214] In yet another embodiment, the antisense oligonucleotide is an a-anomeric oligonucleotide. An a-anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual b-units, the strands run parallel to each other (Gautier et al., Nucl. Acids Res., 15:6625-6641 (1987)). The oligonucleotide is a 2'-O-methylribonucleotide (Inoue et al., Nucl. Acids Res., 15:6131-6148 (1987)), or a chimeric RNA-DNA analogue (Inoue et al., FEBS Lett. 215:327-330 (1987)).

[1215] Polynucleotides of the invention may be synthesized by standard methods known in the art, e.g. by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligonucleotides may be synthesized by the method of Stein et al. (Nucl. Acids Res., 16:3209 (1988)), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., Proc. Natl. Acad. Sci. U.S.A., 85:7448-7451 (1988)), etc.

[1216] While antisense nucleotides complementary to the coding region sequence of the invention could be used, those complementary to the transcribed untranslated region are most preferred.

[1217] Potential antagonists according to the invention also include catalytic RNA, or a ribozyme (See, e.g., PCT International Publication WO 90/11364, published October 4, 1990; Sarver et al, Science, 247:1222-1225 (1990)). While ribozymes that cleave mRNA at site specific recognition sequences can be used to destroy mRNAs

corresponding to the polynucleotides of the invention, the use of hammerhead ribozymes is preferred. Hammerhead ribozymes cleave mRNAs at locations dictated by flanking regions that form complementary base pairs with the target mRNA. The sole requirement is that the target mRNA have the following sequence of two bases: 5' -UG-3'. The construction and production of hammerhead ribozymes is well known in the art and is described more fully in Haseloff and Gerlach, *Nature*, 334:585-591 (1988). There are numerous potential hammerhead ribozyme cleavage sites within each nucleotide sequence disclosed in the sequence listing. Preferably, the ribozyme is engineered so that the cleavage recognition site is located near the 5' end of the mRNA corresponding to the polynucleotides of the invention; i.e., to increase efficiency and minimize the intracellular accumulation of non-functional mRNA transcripts.

[1218] As in the antisense approach, the ribozymes of the invention can be composed of modified oligonucleotides (e.g. for improved stability, targeting, etc.) and should be delivered to cells which express the polynucleotides of the invention in vivo. DNA constructs encoding the ribozyme may be introduced into the cell in the same manner as described above for the introduction of antisense encoding DNA. A preferred method of delivery involves using a DNA construct "encoding" the ribozyme under the control of a strong constitutive promoter, such as, for example, pol III or pol II promoter, so that transfected cells will produce sufficient quantities of the ribozyme to destroy endogenous messages and inhibit translation. Since ribozymes unlike antisense molecules, are catalytic, a lower intracellular concentration is required for efficiency.

[1219] Antagonist/agonist compounds may be employed to inhibit the cell growth and proliferation effects of the polypeptides of the present invention on neoplastic cells and tissues, i.e. stimulation of angiogenesis of tumors, and, therefore, retard or prevent abnormal cellular growth and proliferation, for example, in tumor formation or growth.

[1220] The antagonist/agonist may also be employed to prevent hyper-vascular diseases, and prevent the proliferation of epithelial lens cells after extracapsular cataract surgery. Prevention of the mitogenic activity of the polypeptides of the

present invention may also be desirous in cases such as restenosis after balloon angioplasty.

[1221] The antagonist/agonist may also be employed to prevent the growth of scar tissue during wound healing.

[1222] The antagonist/agonist may also be employed to treat, prevent, and/or diagnose the diseases described herein.

[1223] Thus, the invention provides a method of treating or preventing diseases, disorders, and/or conditions, including but not limited to the diseases, disorders, and/or conditions listed throughout this application, associated with overexpression of a polynucleotide of the present invention by administering to a patient (a) an antisense molecule directed to the polynucleotide of the present invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention.

invention, and/or (b) a ribozyme directed to the polynucleotide of the present invention

**[1224] Other Activities**

[1225] The polypeptide of the present invention, as a result of the ability to stimulate vascular endothelial cell growth, may be employed in treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as thrombosis, arteriosclerosis, and other cardiovascular conditions. These polypeptide may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

[1226] The polypeptide may also be employed for treating wounds due to injuries, burns, post-operative tissue repair, and ulcers since they are mitogenic to various cells of different origins, such as fibroblast cells and skeletal muscle cells, and therefore, facilitate the repair or replacement of damaged or diseased tissue.

[1227] The polypeptide of the present invention may also be employed stimulate neuronal growth and to treat, prevent, and/or diagnose neuronal damage which occurs in certain neuronal disorders or neuro-degenerative conditions such as Alzheimer's disease, Parkinson's disease, and AIDS-related complex. The polypeptide of the invention may have the ability to stimulate chondrocyte growth, therefore, they may

be employed to enhance bone and periodontal regeneration and aid in tissue transplants or bone grafts.

[1228] The polypeptide of the present invention may be also be employed to prevent skin aging due to sunburn by stimulating keratinocyte growth.

[1229] The polypeptide of the invention may also be employed for preventing hair loss, since FGF family members activate hair-forming cells and promotes melanocyte growth. Along the same lines, the polypeptides of the present invention may be employed to stimulate growth and differentiation of hematopoietic cells and bone marrow cells when used in combination with other cytokines.

[1230] The polypeptide of the invention may also be employed to maintain organs before transplantation or for supporting cell culture of primary tissues.

[1231] The polypeptide of the present invention may also be employed for inducing tissue of mesodermal origin to differentiate in early embryos.

[1232] The polypeptide or polynucleotides and/or agonist or antagonists of the present invention may also increase or decrease the differentiation or proliferation of embryonic stem cells, besides, as discussed above, hematopoietic lineage.

[1233] The polypeptide or polynucleotides and/or agonist or antagonists of the present invention may also be used to modulate mammalian characteristics, such as body height, weight, hair color, eye color, skin, percentage of adipose tissue, pigmentation, size, and shape (e.g., cosmetic surgery). Similarly, polypeptides or polynucleotides and/or agonist or antagonists of the present invention may be used to modulate mammalian metabolism affecting catabolism, anabolism, processing, utilization, and storage of energy.

[1234] Polypeptide or polynucleotides and/or agonist or antagonists of the present invention may be used to change a mammal's mental state or physical state by influencing biorhythms, cardiac rhythms, depression (including depressive diseases, disorders, and/or conditions), tendency for violence, tolerance for pain, reproductive capabilities (preferably by Activin or Inhibin-like activity), hormonal or endocrine levels, appetite, libido, memory, stress, or other cognitive qualities.

[1235] Polypeptide or polynucleotides and/or agonist or antagonists of the present invention may also be used as a food additive or preservative, such as to increase or

decrease storage capabilities, fat content, lipid, protein, carbohydrate, vitamins, minerals, cofactors or other nutritional components.

**[1236] Other Preferred Embodiments**

[1237] Other preferred embodiments of the claimed invention include an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 50 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1.

[1238] Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Clone Sequence and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

[1239] Also preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the Start Codon and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

[1240] Similarly preferred is a nucleic acid molecule wherein said sequence of contiguous nucleotides is included in the nucleotide sequence of SEQ ID NO:X in the range of positions beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

[1241] Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 150 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.

[1242] Further preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least about 500 contiguous nucleotides in the nucleotide sequence of SEQ ID NO:X.



[1243] A further preferred embodiment is a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the nucleotide sequence of SEQ ID NO:X beginning with the nucleotide at about the position of the 5' Nucleotide of the First Amino Acid of the Signal Peptide and ending with the nucleotide at about the position of the 3' Nucleotide of the Clone Sequence as defined for SEQ ID NO:X in Table 1.

[1244] A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence of SEQ ID NO:X.

[1245] Also preferred is an isolated nucleic acid molecule which hybridizes under stringent hybridization conditions to a nucleic acid molecule, wherein said nucleic acid molecule which hybridizes does not hybridize under stringent hybridization conditions to a nucleic acid molecule having a nucleotide sequence consisting of only A residues or of only T residues.

[1246] Also preferred is a composition of matter comprising a DNA molecule which comprises a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the material deposited with the American Type Culture Collection and given the ATCC Deposit Number shown in Table 1 for said cDNA Clone Identifier.

[1247] Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in the nucleotide sequence of a human cDNA clone identified by a cDNA Clone Identifier in Table 1, which DNA molecule is contained in the deposit given the ATCC Deposit Number shown in Table 1.

[1248] Also preferred is an isolated nucleic acid molecule, wherein said sequence of at least 50 contiguous nucleotides is included in the nucleotide sequence of the complete open reading frame sequence encoded by said human cDNA clone.

[1249] Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 150 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

**[1250]** A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to sequence of at least 500 contiguous nucleotides in the nucleotide sequence encoded by said human cDNA clone.

**[1251]** A further preferred embodiment is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to the complete nucleotide sequence encoded by said human cDNA clone.

**[1252]** A further preferred embodiment is a method for detecting in a biological sample a nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing a nucleotide sequence of at least one nucleic acid molecule in said sample with a sequence selected from said group and determining whether the sequence of said nucleic acid molecule in said sample is at least 95% identical to said selected sequence.

**[1253]** Also preferred is the above method wherein said step of comparing sequences comprises determining the extent of nucleic acid hybridization between nucleic acid molecules in said sample and a nucleic acid molecule comprising said sequence selected from said group. Similarly, also preferred is the above method wherein said step of comparing sequences is performed by comparing the nucleotide sequence determined from a nucleic acid molecule in said sample with said sequence selected from said group. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

**[1254]** A further preferred embodiment is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting nucleic acid molecules in said sample, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X

wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

**[1255]** The method for identifying the species, tissue or cell type of a biological sample can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

**[1256]** Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject nucleic acid molecules, if any, comprising a nucleotide sequence that is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

**[1257]** The method for diagnosing a pathological condition can comprise a step of detecting nucleic acid molecules comprising a nucleotide sequence in a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from said group.

**[1258]** Also preferred is a composition of matter comprising isolated nucleic acid molecules wherein the nucleotide sequences of said nucleic acid molecules comprise a panel of at least two nucleotide sequences, wherein at least one sequence in said panel is at least 95% identical to a sequence of at least 50 contiguous nucleotides in a sequence selected from the group consisting of: a nucleotide sequence of SEQ ID NO:X wherein X is any integer as defined in Table 1; and a nucleotide sequence encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1

and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The nucleic acid molecules can comprise DNA molecules or RNA molecules.

**[1259]** Also preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1.

**[1260]** Also preferred is a polypeptide, wherein said sequence of contiguous amino acids is included in the amino acid sequence of SEQ ID NO:Y in the range of positions beginning with the residue at about the position of the First Amino Acid of the Secreted Portion and ending with the residue at about the Last Amino Acid of the Open Reading Frame as set forth for SEQ ID NO:Y in Table 1.

**[1261]** Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

**[1262]** Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of SEQ ID NO:Y.

**[1263]** Further preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the complete amino acid sequence of SEQ ID NO:Y.

**[1264]** Further preferred is an isolated polypeptide comprising an amino acid sequence at least 90% identical to a sequence of at least about 10 contiguous amino acids in the complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

**[1265]** Also preferred is a polypeptide wherein said sequence of contiguous amino acids is included in the amino acid sequence of a secreted portion of the secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

**[1266]** Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 30 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

**[1267]** Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to a sequence of at least about 100 contiguous amino acids in the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

**[1268]** Also preferred is an isolated polypeptide comprising an amino acid sequence at least 95% identical to the amino acid sequence of the secreted portion of the protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

**[1269]** Further preferred is an isolated antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

**[1270]** Further preferred is a method for detecting in a biological sample a polypeptide comprising an amino acid sequence which is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1; which method comprises a step of comparing an amino acid sequence of at least

one polypeptide molecule in said sample with a sequence selected from said group and determining whether the sequence of said polypeptide molecule in said sample is at least 90% identical to said sequence of at least 10 contiguous amino acids.

[1271] Also preferred is the above method wherein said step of comparing an amino acid sequence of at least one polypeptide molecule in said sample with a sequence selected from said group comprises determining the extent of specific binding of polypeptides in said sample to an antibody which binds specifically to a polypeptide comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

[1272] Also preferred is the above method wherein said step of comparing sequences is performed by comparing the amino acid sequence determined from a polypeptide molecule in said sample with said sequence selected from said group.

[1273] Also preferred is a method for identifying the species, tissue or cell type of a biological sample which method comprises a step of detecting polypeptide molecules in said sample, if any, comprising an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

[1274] Also preferred is the above method for identifying the species, tissue or cell type of a biological sample, which method comprises a step of detecting polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the above group.

[1275] Also preferred is a method for diagnosing in a subject a pathological condition associated with abnormal structure or expression of a gene encoding a secreted protein identified in Table 1, which method comprises a step of detecting in a biological sample obtained from said subject polypeptide molecules comprising an amino acid sequence in a panel of at least two amino acid sequences, wherein at least one sequence in said panel is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

[1276] In any of these methods, the step of detecting said polypeptide molecules includes using an antibody.

[1277] Also preferred is an isolated nucleic acid molecule comprising a nucleotide sequence which is at least 95% identical to a nucleotide sequence encoding a polypeptide wherein said polypeptide comprises an amino acid sequence that is at least 90% identical to a sequence of at least 10 contiguous amino acids in a sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

[1278] Also preferred is an isolated nucleic acid molecule, wherein said nucleotide sequence encoding a polypeptide has been optimized for expression of said polypeptide in a prokaryotic host.

[1279] Also preferred is an isolated nucleic acid molecule, wherein said polypeptide comprises an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y wherein Y is any integer as defined in Table 1; and a complete amino acid sequence of a secreted protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1.

**[1280]** Further preferred is a method of making a recombinant vector comprising inserting any of the above isolated nucleic acid molecule into a vector. Also preferred is the recombinant vector produced by this method. Also preferred is a method of making a recombinant host cell comprising introducing the vector into a host cell, as well as the recombinant host cell produced by this method.

**[1281]** Also preferred is a method of making an isolated polypeptide comprising culturing this recombinant host cell under conditions such that said polypeptide is expressed and recovering said polypeptide. Also preferred is this method of making an isolated polypeptide, wherein said recombinant host cell is a eukaryotic cell and said polypeptide is a secreted portion of a human secreted protein comprising an amino acid sequence selected from the group consisting of: an amino acid sequence of SEQ ID NO:Y beginning with the residue at the position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y wherein Y is an integer set forth in Table 1 and said position of the First Amino Acid of the Secreted Portion of SEQ ID NO:Y is defined in Table 1; and an amino acid sequence of a secreted portion of a protein encoded by a human cDNA clone identified by a cDNA Clone Identifier in Table 1 and contained in the deposit with the ATCC Deposit Number shown for said cDNA clone in Table 1. The isolated polypeptide produced by this method is also preferred.

**[1282]** Also preferred is a method of treatment of an individual in need of an increased level of a secreted protein activity, which method comprises administering to such an individual a pharmaceutical composition comprising an amount of an isolated polypeptide, polynucleotide, or antibody of the claimed invention effective to increase the level of said protein activity in said individual.

**[1283]** The above-recited applications have uses in a wide variety of hosts. Such hosts include, but are not limited to, human, murine, rabbit, goat, guinea pig, camel, horse, mouse, rat, hamster, pig, micro-pig, chicken, goat, cow, sheep, dog, cat, non-human primate, and human. In specific embodiments, the host is a mouse, rabbit, goat, guinea pig, chicken, rat, hamster, pig, sheep, dog or cat. In preferred embodiments, the host is a mammal. In most preferred embodiments, the host is a human.



**[1284]** In specific embodiments of the invention, for each "Contig ID" listed in the fourth column of Table 6, preferably excluded are one or more polynucleotides comprising, or alternatively consisting of, a nucleotide sequence referenced in the fifth column of Table 6 and described by the general formula of a-b, whereas a and b are uniquely determined for the corresponding SEQ ID NO:X referred to in column 3 of Table 6. Further specific embodiments are directed to polynucleotide sequences excluding one, two, three, four, or more of the specific polynucleotide sequences referred to in the fifth column of Table 6. In no way is this listing meant to encompass all of the sequences which may be excluded by the general formula, it is just a representative example. All references available through these accessions are hereby incorporated by reference in their entirety.

**Table 6**

Clone ID NO.:Z	SEQ ID NO.:X	Contig ID: 665424	Accession #'s
HKABZ65	11		AA715814, AA503019, AW338860, AL044701, AA715173, AA715075, AF568659, AA525144, AF109907, AC005071, AC004878, AC005081, AC002549, AC020663, AC006064, AC004858, AC007666, AL022318, AL035086, AC004656, AC004067, AC004477, AC006023, Z98884, AC007637, AL080243, AC002369, Z84487, AL031311, AL049776, AC004686, AL080317, AC002310, AL050318, AL132712, D87675, AC007546, AC004675, AL035683, AC002288, AF030453, Z95331, AC006077, AC008101, AF088219, AC005175, AL021391, AC005670, AL133163, AL031123, AC004770, AC004659, AL078463, AC002492, AC006084, AC005089, AL031670, AC005088, AC004491, AC005887, AP000008, AC002457, AC009946, AC005200, AC006581, AL022316, AC005180, AC005015, AP000553, Z98742, AC007283, AC005920, AC004832, AL035462, AC002352, AC005037, AF111169, AC004854, AF067844, U95090, AL109623, AF053356, U78027, Z85987, AP000704, AC004263, AC004232, AC005661, AC005409, AF000563, AC005005, AL031848, AC004881, AC004685, AC005480, AC003950, AC000026, AC007563, AL021155, AC002470, AL031767, AP000557, Z73358, AL023553, AC002375, U52112, AC002395, AC002425, AC005280, AC006101, AL034418, AC005538, AC002476, AL049569, AL109801, AL035422, AC005102, AC002059, Z85996, AC004813, Z98304, AC003663, AC005562, AL034402, AC004804, AC002477, AC007225, AC005399, AL121825, AL034421, AL008718, Z84486, AC007051, AC005366, Z98950, AL049795, AC002073, AC006536, AC004905, AL035405, AC004587, U91327, AL096791, AC005393, AP000513, AL109753, AC003029, AL021918, AC005703, AL035659, Z93020, and AL031279.
HNGIC80	12	637909	AL118503
HDPUG50	13	684120	AI217895, AI983150, AW385698, AW374106, AI660124, AI339010, AW374124, AI166971, AA542906, AA689356, AI285269, AI346870, N27706, AW236815, AI821227, AI821074, AL134542, AI166818, AA836112, D20721, AI221030, AA627350, AW027663, N35710, AI221246, AW372396, AI285231, T95430, AW372395, AI699709, AL134543, AA055338, AA449417, AW197834, R83129, AI418208, AA375954, AA450383, AA961046, N20259, AA336834, AA226636, AI911109, AA225691, N20865, AA825421, AI932769, AA938413, AW197872, AA370379, N29162, C03633, AI620095, AA055337, AI932771, AA976076, AI821821, AA173926, AA173884, AA569611, AI821883, AA772955, AW383971, AI432644, AI431307, AI431316, AI432666, AI431238, AI623302, AI432653, AI431323, AI921241, AI431347, AI431350, AI432655, AW081103, AI431321, AL042853, AL042729, AI431243, AI431230, AI431328, AI432654, AI431310, AI431312, AI432650, AI432677, AI431247, AI432657, AI492519, AI431231, AI791349, AI431257, AI431235, AI431315, AI431354, AI431318, AI431353, AI432661, AI431246, AI432649, AI432643, AI432675, AI431337, AI432651, AI432647, AI432674, AI431330, AW129223, AL045327, AI431248, AL042931, AI432665, AL042519, AI224875, Y17793, AF019249, AL133082, and AF064854.
HAEAB66	14	580083	AI659421, AI632698, AI969812, AI394313, AW139577, AI739006, AW271206, AW293868, AI805043, AI799897, AI923366, AA640596, AA308562, H80192, AA833662, AA910928, AI275400, AW377553, AW377527, AI191675, AI041565, AW138256, AI693984, AI392758, AI597816, AA776304, AI956051, AI085021, AI288918, AI076685, AA725434, AI824191, AI471844, AA524228, N70113, AA143492, AA143493, AA226122, AA226045, AI123234, AA858158, AA532806, W01829, N70775, AI183697, AI693773, AA757995, AA304772, H78816, AI276951, AA613815, AA152444, AI076680, AI283120, AA152445, AF228603, AF157600, and AF170564.
HHEPF59	15	695722	AL120852, AI9222659, AA932542, AA262051, AA526382, AW205846, N39596, AI459931, AW406797, AI866992, AI373687, AI475825,

AA582869, AI862875, AA223668, R96889, T90824, AA642941, R43602, D60935, R44585, AA812110, AI669230, AI928028, AI199166, AI369241, AI799999, AI963565, N52647, D80065, N68066, R96890, AI083867, T85729, R19318, N80503, AW451196, N72375, AI571518, AI797299, AI685620, AW002004, AW194849, AW197067, AI498711, N46743, AW243761, AA974737, AW189464, AI383927, T23990, AI373614, AI633402, AA247241, AI961589, AI120853, AI587156, AI702073, AI537261, AI862139, AI500714, AI627988, AI921248, AI433157, AI633125, AW084425, AI659585, AI677796, AI121564, AI277008, AI677797, AI277009, AI670009, AI280637, AI873923, AI620003, AI570989, AW029638, AI590630, AI812107, AW129271, AI620089, AI963193, AI281772, AI624293, AW105383, AI683173, AI682971, AI745656, AW080327, AI874166, AI86181, AI637584, AI637584, AI241923, AW090550, AW029329, AW170635, AI610770, AI587114, AI500061, AI583085, AI564719, AI469532, AI538564, AI432030, AI499285, AI827154, AI633000, AI538829, AI445025, AI434223, AW148536, AI002285, AI541056, AW129722, AI884318, AI554186, AI357940, AI569637, AI568138, AI445992, AI582932, AW151714, AI521560, AI569975, AA641818, AI287233, AI473536, AW104724, AI866469, AA502794, AW162194, AW104827, AI932949, AI288285, AW192652, AW026087, AI148272, AI591387, AI631095, AI800155, AI610690, AI275640, AI669459, AW149925, AI915291, AI963346, AW148408, AI499393, AI469112, AW193530, AW073270, AI632408, AW090071, AI866801, AI690426, AW058243, AL048656, AW087207, AI499986, AI368868, AI635067, AW081653, AI801152, AI540382, AI890507, AI921464, AI690748, AI521103, AW148363, AW130068, AW051088, AI309244, AI290154, AI362347, AW105431, AI698391, AI142101, AI471909, AI355779, AW190194, AW090736, AI476478, AI922561, AI889189, AA805434, AW008353, AI362248, AI687362, AI037454, AI889376, AI609375, AL039086, AI619426, AW151893, AI744988, AA983883, AI796743, AW162118, AI538716, AI499947, AI648567, W74529, AI280732, AI797538, AI242248, AW075667, AI978703, AI696829, AI249877, AI648508, AW167021, AI046595, AI254731, AI540674, AW132056, AI624084, AI287793, AI569583, AI522052, AI539800, AI579901, AI760435, AW087160, AW193231, AW129916, AI269205, AI933589, AI963458, AW129230, AI925502, AW169604, AI340982, AL037030, AI520862, AW264727, AL040241, AW150453, AW262552, AI568855, AI286256, AW169653, AI261344, AW263823, AW168788, AC004596, AF090901, E05822, I89947, AL137429, AL133112, AR038854, AL137523, AL137539, AF061981, AL050116, I48978, AL137459, AC004883, AL133072, AL137480, AL050149, AL078630, AL110280, A08910, A08909, A08908, Z82022, A08916, A77033, A77035, AF106657, E12747, AF113019, Y10936, AJ000937, A08913, U35846, AL049938, AL049452, AF185576, AI18788, AF026816, AL049283, I33392, AF111849, AC004093, U80742, AL117435, AJ006417, A21103, S36676, AL080159, AF183393, AL122100, AL137529, AF106862, L19437, A08912, AL137463, AB016226, AL137488, AF061573, AC006840, AC005968, I89931, AB022159, AL117416, Y14314, I49625, I48979, A08912, AL137463, AB016226, X82434, AF118094, AL137560, U53505, A49139, AF026124, AL080148, A58524, A58523, AI18777, AL050366, AL117648, AF067790, AF153205, AF109906, AF139986, AL050092, AF008439, AL137557, A07647, L31396, X52034, L31397, X81464, AF182215, AR020905, X87582, Y11254, AL133080, AL049466, X94372, AL137550, S77771, AL122093, AL133113, AL133031, AL050277, AF067728, AF087943, AL137271, E02349, A93350, U87620, AL137533, AL050138, AL133606, AF032666, AJ005690, I89934, AF119337, AL133067, AL133640, I03321, AL133075, M27260, AP000020, AL137476, Y10655, A08907, AC004227, AF090903, I68732, AF177401, D83032, Y10080, AL122110, X79812, AL049430, AF031147, AL117457, AL096744, A03736, AF100931, A65341, AF111851, U58996, AL110197, AF159615, AL110221, U66274, I09499, AL137547, S76508, U88966, E01573, E02319, AL080124, AL050146, AF091084, AF113677, U67958, AL080154, AF079763, I17544, E01314, A45787, X57961, AL117440, AL110225, AL137292, Z97214, AL137276, AF054599, AF126247, AF175903, AF097996, AL133558, AL050024, AF113699, Y09972, AL023657, AF125948, AF162270, Y07905, U42766, X96540, AL110218, X72889, Y09885, E03348, AL049300, AL110296, AL117583, AJ238278, E08631, AF090896, A23630, AL110222, A08911, AI5345, AC002467, AL137283, Y11587, AF118070, AL049382, AL049314, AF106827, I17767, AF142672, Z37987, E07108, AF061795, AF151685, AL050108, AL133665, AL133010, AL137521, X89102, AL137479, X53587, AR011880, I89944, AF090934, L13297, AL137478, AL110196, AL133081, AF210052, A08915, AF158248, L04504, X98834, AL049465, AL133560, L04849, AF003737, AF113690, AF031903, AF017437, AF113689, AL080074, I26207, E04233, AR038969, AL122050, and AF051325.			
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HE9BK23	16	675382	AW299658, AW058550, AI796131, AW299514, AI767984, AI634858, AW235128, AI498692, AI373251, AI796532, R86161, AW295829, T73510, T73442, N71226, C15737, and AF152562.
HCYBI36	17	666358	AI801638, AW089881, AA484795, AI700113, AI452474, AI220875, H03348, T79392, AA305424, H04030, AI392810, AA375432, AW366425, H95362, AI950113, AA375883, AF101051, AF115546, and AF072127.
HSDX51	18	566879	AI792073, AI791928, AW206230, AA317765, R60584, H22857, AI694498, F03192, R05669, AA365484, and U78304.
HSDAJ46	19	692358	AI800075, AI686505, AW023374, AA418208, H97489, AA620395, AA418073, AW027850, AA401879, N67776, AI168759, N36146, AA700811, N28007, AA012999, H99095, AI015805, H82563, H60753, R87427, H59689, AA688368, W03403, H83666, R85022, AI582759, AA205528, H83667, N35665, AA322820, AW072108, H60754, R07653, AA339201, H59688, R07706, N26551, N69337, H84836, N88280, AA640177, AA221012, AA094140, and AB025904.
HRACG45	20	671767	AL043880, AW005102, AA137033, AA523117, AA810411, AI671452, AI339682, AA437080, W90768, AI091057, AI288535, AA528033, AA137115, AW130160, AI338926, AI683304, AI199890, AI625514, AW083986, AW194157, AI859189, AI199896, AI990810, AI269181, AA114896, AA114897, AA922395, AI349372, AI168791, AI812097, AI274942, AA128536, AI266219, W90701, AI636417, AI743815, AI862000, AW204921, R51136, H48319, N78924, AI023431, AA128362, AI305176, AI873659, AI091111, AI056132, AI087400, H48227, R52200, AW339362, AI886641, H79689, R62399, R62400, AI680503, F11141, AA423981, AA938005, AA330985, W05294, M78260, Z46207, AI350674, AI915189, R12869, AA523876, R38443, F08308, R51028, F05074, AA339020, H79690, F08811, AI982566, AA343945, F04534, R43758, AA368664, AW089229, D78779, AA465535, AA368064, AI751158, AW062626, and T05279.
HAPPW30	21	684272	AW341517, AA868388, AA479992, AA305964, AA758865, AI276502, AA846842, AI183515, N41325, AW273135, AA775255, H57026, AA954695, AI337591, AI685296, N95033, AA969117, AI147710, AA962530, AA150989, AA758255, AI675402, AI167695, AI151098, AI798973, AA383301, AW172620, AI359078, AI688288, AI911606, H83172, AI078598, AI188832, H58146, AA446238, AA310796, AA724109, AA864698, AI240610, AA953573, AA421572, H41807, W15373, H48433, AA977855, AA757910, H87382, H46522, AI216014, AA098821, AA877407, W38885, AI739312, R11443, H46521, R19191, H82944, W72627, C04986, AI479980, H56935, AI216655, AA339733, R99133, AA975974, AA922234, AA375160, AW183259, AA421590, AI459843, T61945, AI216656, AI191499, AI902298, H70309, AI902295, T71506, AA150942, AA383302, N57057, AA568552, T62175, R94393, AW021717, AI811212, AI924051, AW411235, AW411351, AW411265, AW410902, AI923989, AW166742, AI284509, AA742505, AA100772, AI804524, AW162189, AI654329, AI244704, AI049850, AI628333, AI343379, AI567204, AI457113, AA585298, T29005, AI889191, AI289436, R42275, AW411298, N63128, AW409775, AI954425, AR037084, AR054173, AI137258, AR068753, S71381, M19658, AR068751, AI133015, Y11254, AF065135, A76337, A76335, I92592, A91160, S68736, A93016, Y10936, AR015970, AF093542, AI137254, AI133560, Y16645, AF118094, AJ132433, E03671, AF139986, U88966, AL096751, AL031903, AL133024, L04504, E08517, AF130470, AL050024, AF081366, S69385, AL050172, AF132341, AC006203, and AC006112.
HE2ESS1	22	684278	AI792241, AI793025, AW242855, AI767568, AA999850, AI911520, AI765078, AI373739, AI793193, AI985237, AI433883, AI478325, AI671437, AI613056, AI253234, AI524824, AI650909, AW299600, AI431850, AA131483, AI470468, AI473091, AA345162, AA065156, AA076448, AA282824, AI134259, AI862043, AI801088, AI583966, AI473471, AI120446, AI520946, W45039, AI035890, AW020619, AI239701, AI741637, AI468959, AA159625, AW410316, AC003669, U83112, AR030544, AF113677, I06996, AI137550, S71381, AR064250, X15132, AF091084, X67813, AL080234, AF113691, AF010191, E15324, AR054173, A23327, A49723, A49722, AB029755, E16086, E13052, U53505, X66417, I29004, AF113690, and A03736.
HAGGI80	23	1158546	
HTXDW56	24	695765	AI765620, AA725071, AW271710, AI916562, AI634990, AI654165, AI991405, AI983985, AW299864, AI670830, AI570128, AW168930, AW009948, AA704525, AI749744, AW000916, AA861614, AI955276, AI492455, AI676055, AI276897, AI681128, AI796805, AW275120,

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HEEAG23	25	684254	AI279852, H57654, AI472339, H85172, AA383569, H96534, AA903404, AA719530, AI084916, AW135894, AA993772, AA890589, W61170, AA807443, AA814409, AI828884, R76166, AA470533, AI829062, AA737653, H96878, R62923, AA714658, AA705115, AI964064, AA569749, AI343340, AA769402, AW080830, AA494452, AI871834, AW193760, AL045053, D58349, AW275510, AI445674, AW168618, AA635739, AI039584, AI656744, AA158461, AA551552, AA490183, AA169263, AC004938, AR052481, AL031777, AL035079, AC004882, AL031680, AL109938, AC006312, AP000223, AL121578, AC005033, AC005082, U63313, AC006511, AC004477, AC006315, Z84572, AL035462, Z83823, AC002350, AC010206, D83253, AC004151, AC005291, AC005225, AC004652, AL021940, AP000962, AL031721, AL031666, AC004167, AL009183, U78027, AL021393, AC004223, AC002400, AF141309, AC006101, AL136297, AL035422, AL022100, AL049643, AC005694, AC003006, AL035659, AL022165, AC007066, AL133448, AL080243, AL137100, AC007014, AC004752, AL031427, Y18000, AC004832, AC003065, AC005800, AC006515, AC006011, AL035587, AC006017, AC004913, AC005387, AP000045, AC002039, AL117258, AC004076, AL031228, AD000092, AC006049, AL121934, AL022316, AC006205, Z82244, AC005393, AC006057, AC007324, AP000228, AC007919, AC007051, AC011718, AC006127, AC007227, AC005696, AC004754, AC004534, Z86090, AF107885, AP000547, AC005488, AP000689, AL035409, AC005037, AL049793, Z97196, AP000140, AC009743, AP000359, AP000088, Z69705, Z98051, Z84816, AF178030, AC002492, AC006211, Z92540, AC005725, AC000387, AC006125, AL033392, Z95116, AC008079, AC000115, AL008725, AC006581, AL133289, AC005776, AL139054, AF141308, AC002347, Z97632, Z93241, Z98752, AC005529, AL022311, AL096707, AL078593, AC010722, AC005323, AL031650, AC006544, AC002476, AC004883, AC004814, AF037338, Z98950, AC006543, AC007358, AL035420, AL109839, AL022238, AC005531, AF196969, AC002299, AL034420, AC004525, AP000104, AF200465, AC004833, AC005913, AL024507, Z93016, AL031577, AC007262, AL049766, AC004130, AC005486, AC002312, AL050308, AL009181, AC006285, AL078474, AL035252, AC006253, AC005632, AF190465, AC004854, AF035396, AL049776, U95740, AF109907, AC005702, AL022163, AC009263, AC007688, AC005829, AC005779, AC005088, AC005060, AC004808, AC004686, AC004057, AC016025, AC005527, AC005228, AC006974, AC007226, AC005512, Z81369, AC005378, AC004690, AC003102, AC005618, Z73359, AL079295, AL022395, U91327, AC018769, AC004673, AF111169, Z95400, AC002300, AC005859, AL035423, AC004675, AF053356, AC003684, AF205588, AL049830, AC004019, AC004463, AL035455, AC008033, AC005736, AC004890, AC002990, AP000552, AL031602, AF106656, AC004933, AD000812, AF064861, AL049757, AC005933, AA252707, and AA252834.
HDPK193	26	683964	AW026665, AI038157, AW160610, AA291566, AI313184, AA513729, AI028306, R72376, AI167786, AI744406, AI185677, AI660416, AA856738, AA397659, AA479875, AI918286, AA479739, W68014, AA628725, AA216390, R62410, AA399031, AW162156, AI032922, W67956, AA229418, AI628273, AA759314, AI564387, AI874106, AA100111, AA852988, AA852989, AA677565, AA627551, AW269334, AI885854, AA100172, AI886985, AI369442, H40744, AI927077, AA188450, N94366, AA291402, AA187325, AI342982, AW136745, AW136249, AI499025, T24752, AI241302, AI990643, AI971492, AI074558, AW166318, AA428682, T55849, AA837459, T18597,

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HDLAC10	27	692299	<p>AL049012, AW161772, AI963569, AI627938, AA430167, AW150904, AA811288, AW148833, AA016001, AA534493, AI580793, AI473859, AA552599, AI762820, AA630256, AI249503, AI289630, AI093700, AI683179, AA902142, R50658, AA994326, Z43651, AI796343, Z39714, T36201, R50558, D60811, AI796404, AW023060, AI560541, AA445981, Z45738, F04619, AF205600, and AF205601.</p>
HDPOH06	28	683371	<p>AI378660, AA669141, AI985796, AA688220, AI042515, AI372881, AI014423, AW025175, AI335099, AW263024, AI491990, AW128917, AI570270, AI128127, R91019, W85883, N59550, AW305279, AA679558, AI635705, AI559984, F00878, AW340645, R08677, W85967, AI262108, T98198, AA670170, T53837, AA337112, AA583164, R88760, AA902605, N78291, T98199, AI540509, AC003108, AC003684, Z95152, AC004694, AC002365, AL121603, AL049872, AC005071, AC007425, and R08585.</p>
HCE4G61	29	846836	<p>AF039237, AL041798, AI831480, AW340563, AW025258, AI127613, AI818249, AA523520, AI750911, AA315462, AI216595, AA564125, AA058690, N24213, AW005271, AI735048, AA677314, AI278958, AA416726, R72506, AA071513, H39933, AI202794, AI871329, AA287126, AI269956, AA045523, C05686, AA040646, AA296927, AW386990, D80945, D61149, R37394, AI261950, Z44618, D60504, AI342287, AA297041, AA323642, AI289604, R85079, AI867501, T35835, R37967, AI021950, R72507, AA082290, AI350532, AI925788, AI369584, AA889809, AA297013, AW105104, AW391339, Z40486, R08860, R13486, R72016, AI188886, AI784381, AI186121, F01836, AA977138, AA534946, C15524, AA327396, AA057306, AA058536, Z42306, AI801558, AA416805, AI631998, AI750912, D31575, R72047, R72058, and AC004596.</p>
HCWUI13	30	695679	
HDPSF01	31	689129	<p>AI871101, AI560217, AA047000, AW190726, AA419038, AI479404, AA035467, AI361637, AI198435, AA725194, AI093316, AA442664, AI078128, AI274339, AA915909, AI677732, AI283200, AI769275, AI857306, AI275083, AA423792, AA046943, AI291474, AI291805, AI983969, AA427407, AA661657, AI141350, AA031475, N92812, W24931, AA035466, AA031617, AA961077, AA250784, AW070742, AA411122, AA378564, AW051192, AW452102, AW293787, H91665, AA514348, AW149476, H91759, T86488, AW392670, Z99396, AL119363, U46347, AL119457, AW363220, AW384394, AL119497, AL119319, AL119444, AW372827, AL119443, U46350, U46351, U46349, AL119324, AL119484, AL119391, AL119355, AL119483, AL119439, U46346, U46341, AL134525, AL134533, AL119341, AL119335, AL119522, AL037205, AL119418, AL134528, AL119399, AL134531, AL134527, AL134538, U46345, AL119396, AL119496, AL042614, AL043003, AI142134, AL042542, AL042544, AL042450, AL043019, AL042984, AL042965, AL042975, AL043029, AL119304, AL042551, AL119464, AB026436, AR054110, AR060234, A81671, AR066494, and AR069079.</p>
HHPEN62	32	695134	<p>AI939620, AI480056, AW300615, AW300620, AI589129, AI911546, AI361251, AI498527, H41544, AA326679, AA348503, AI422476, AA912288, and AI423129.</p>
HUKBT29	33	694590	<p>AI889172, AI080136, AA211445, AA211523, F24617, AA211502, F27978, AI862904, F28119, F30666, F29048, AI972919, AA211549, AI128717, Z24989, AW302460, F28086, F26294, Z28706, AA413432, and R45814.</p>
HMAJR50	34	654004	<p>AW408305, AW403731, AW117933, AA947938, AW268857, AI983988, AI566347, AW129984, AW051493, AI741765, AI803337, AW081302, AI811384, AI828939, AL037800, AI146996, AA720675, N21132, AI419827, AI460230, AI080555, AW195872, AI348121, AA833715, AW193550, AI285275, N31147, H97793, AW189406, AI240056, AI806449, AA928209, AW277257, AI225247, N50918, AA907019, AI597972, AW302355, AI050898, H82455, AA364171, AI610240, AI376029, AI989465, AA746601, R68913, AA157064, N21022, N47537, AW087619, Z44334, AA156969, H10287, AW197890, AA047176, AI074218, H59319, H13601, AI613266,</p>

		T35974, R19227, A1338148, A1281563, AA992483, T35248, N42759, T34340, R59345, R62736, T30641, D56630, H10230, W02661, N31923, R38953, R19536, AA995898, T80302, AA248245, N67312, R68809, A1355476, R21115, AA694574, AA904354, Z40284, R59344, R45755, D56961, T34357, T35247, AA313414, T30099, AA301358, A1277161, T31945, T32601, A1865075, R44491, R43889, AA906085, A1560586, T36242, AA585150, N83938, AW197781, A1824759, W25731, Z28514, H59272, R78516, R29225, A1798671, N47536, AW378845, T24535, AA057047, A1583065, A1619777, A1312428, A1923989, A1045266, A1288305, A1866573, A1590043, A1538885, A1335426, A1348777, A1500061, A1432969, A1287326, A1866465, A1468872, A1682798, A1433157, AA572758, A1702073, A119836, A1887308, A1539771, A1500523, A1582932, A1249877, A1040241, A1698391, A1815232, A1915291, A1874261, A1207656, AA420722, A1819326, A1889189, A1079963, A1608936, A1799273, A1340603, AA420758, AW163834, A1038605, AW129230, A1675052, A1637584, A1798404, A1041150, A1625464, A1872910, AW161579, A1539153, A1632408, AW118496, A1570989, A1499986, AW102924, A1570861, A1110306, AW410969, A1929108, AW190042, AW087462, A1866770, A1037521, A1633419, A1345347, A1176980, A1446373, A1340533, A1045500, AW088903, AA635382, AW151136, AW148536, A1538085, A1801325, AW022682, A1345608, AW051056, A1036403, A1284517, AW409914, A1697045, A1783504, A1538342, A1572021, A1863082, AW151485, A1288285, A121014, A1036802, A1635067, AW411235, A1580435, A1048656, A1473799, A1036396, A1039086, A1038565, A1890214, A1119791, AW166903, AW059713, A1611738, A1963194, A1270099, A1251221, A1801793, A1340519, N33175, A1471909, A1352497, A1631273, A1571439, A1619748, A1500706, A1537677, A1934035, A1521560, A1500662, A1345745, A1623396, A1927233, A1036541, AA579232, A1888661, A1539687, A1475430, A1445992, A1135022, A131856, AF195141, AC005915, E07108, Y11587, I48978, AF090901, AF090903, I89947, AF067728, A08916, A08913, I00734, A08910, A08909, A117460, AF158248, AF106862, E03348, AF177401, AF113677, Z82022, I48979, A1133067, A1049283, E00617, E00717, E00778, E02349, AF017152, A65341, Y11254, S68736, X65873, A93016, I89931, A1049382, AF078844, I49625, A1133080, A1137271, A1133075, A1137550, A1137557, I61429, A110228, AF090934, A1080159, Y14314, A1122093, U35846, U80742, AF113019, A1133014, A1133072, S78214, A1133560, Y16645, A110196, A77033, A77035, AF125949, X93495, AF079765, A122050, AF087943, A1117457, A1050116, I17767, A1137533, A1117585, AF090896, AF106657, E05822, I42402, A1238278, AF039137, A1137283, A1080074, AF118090, AF111851, A1137459, A1050149, A1096744, A1122121, A1080060, AF091084, A1050024, AF183393, A1117435, AF1104032, AF061943, AF113013, A1050393, S61953, A1122110, A1136884, A1000937, A1049430, AF107847, A1137281, AF125948, A1080124, AB019565, X82434, A1049452, AF118094, A117463, A1117583, AF153205, A93350, A137656, A03736, A1049938, I26207, I33392, AF113699, AF090900, A1117394, X98834, AF113691, A65340, AR038969, A1110221, A08912, A1050108, A1110225, A1133113, A1050138, A1133606, E15569, A58524, A58523, E01573, E02319, AF119337, AF008439, AF118070, I03321, AF146568, A1050092, U42766, A1122123, A1049466, A1050146, AR020905, A1133104, AF113690, AF113689, U67958, AF113676, U73682, A1012755, U72620, X72889, X53587, A1049314, AR011880, A08911, A1050277, AR000496, U39656, AF141289, A1133077, A1137521, X63574, AF026816, A18777, I09360, AF106827, A122098, A1137527, A1133565, AR059958, E08263, E08264, U00763, AF114168, AF113694, AF017437, AF097996, A1137560, A1133640, X84990, AF026124, A1133016, I09499, A1137548, S76508, X96540, AR038854, A1137463, Y10655, AF145233, A1137538, S83440, A1110280, AF111112, A1049464, AF069506, A1242859, AF111849, A1137554, A1133557, AF126488, Y09972, E08631, L31396, A1117440, AF185576, A12297, A1133031, L31397, A1110159, AF090943, AF118064, A1133093, L40363, X70685, Z72491, A1137648, A1080127, A1080137, AR068753, E07361, AF000145, A1137556, A1122049, X79812, U58996, U87620, U89295, A08907, AF207750, A08908, A1050172, AF079763, AB007812, I92592, Z37987, I66342, U72621, Y07905, AR068751, A76335, AF120268, S53987, D16301, A1137480, and AA075938.	
HBIMB51	35	672711	AW293249.
HE8DX88	36	663511	A1352035, and A1049871.

HNGHT03	37	692430	N58127, AI970999, AA543049, AA805508, AA481100, AW086144, AI224173, N52797, N49240, AW439223, AA480173, W87476, AA481045, AI702077, AA968423, AI208249, AA676568, AI339421, AA551673, H61729, H90630, AA354107, H18441, H90534, AA203228, Z41571, AA948533, AI990383, H24029, H18549, H22748, H61939, AW075792, W87571, AI270746, AA002111, AA002112, AW072594, N57619, AA977512, AL043010, AF092094, AF155157, and AF004231.
HDTAT90	39	692291	AL041807, AA315553, AA578538, R60726, AA578520, W25198, N34727, AW160746, R90863, R84524, AW246146, AA081697, T52130, AW177731, AI525011, AW177733, AW068182, C04045, R51326, AA251576, AA081290, and AL050275.
HHFGR93	40	691402	AW190823, W52782, AI921717, AA707399, AA780017, AI809901, AI656071, AI870870, AI633244, AA046658, AA913618, AA428298, AI014541, AW300019, AW173046, H12307, AA428713, H12782, AI141481, AI092488, W58612, AW172540, AI184646, W58613, AI359381, AW361707, AI126255, R77354, AI970137, AI949837, AW081182, AI923177, AI187105, AI624748, R69232, AA514466, AI521359, R69114, AI347221, R76149, AA664044, R73827, R79810, H12841, R78260, H12629, R76098, R63063, R32862, R78261, T47327, AI189377, R73853, R62315, R68433, AI828342, H12360, AA618505, H12680, T50332, R79923, R79910, AI216465, AA733001, R35438, AA683601, AW009057, R81664, T98690, H00855, R33685, H02334, AI189455, R73852, AW365832, AI873711, R67936, H02440, AI569353, H02804, R68432, R66838, H38189, R76065, R64387, R33581, R35749, AW235425, T98640, R27675, AA991630, AI189443, R75889, R81467, R31360, AA367816, R27576, R63218, AA359117, R31889, R34252, AI762218, AW002259, W52486, H01235, AI199859, R62314, AA046788, AA249358, R64386, AW407088, N55686, R67441, AI002022, D45691, AA446485, AA430177, AI432644, AI492519, AI623302, AI432655, AI432661, AI432653, AI431354, AI431312, AI431347, AI431230, AI431328, AI432654, AI431310, AW081103, AI432677, AI431337, AI431351, AI432675, AI431353, AW128900, AI432674, AI432651, AI432647, AI431330, AI431243, AI432650, AI431248, AI431255, AI431307, AI431316, AI432649, AI432672, AI432665, AI431254, AI431357, AI432662, AI431241, AI791349, AI432676, AI431345, AI431346, AI432673, AI432658, AI432666, AI431340, AI431238, AW128846, AI432664, AI431308, AI432657, AI432645, AI431321, AI431247, AW128897, AI431231, AI432643, AI431257, AI431323, AI431350, AI431318, AW128884, AI431235, AI431315, AI492520, AI492510, AI431246, AI431751, AI492509, AW129223, AI431314, AL042729, AL042931, Y17793, AF064854, and AF019249.
HOVCB25	41	691357	AA318972, AB014534, AF116574, AF116573, AC000029, and AC003678.
HSYAV66	42	686437	AF126372.
HPFCT29	43	668239	
HAWAT25	44	677480	AI992139, AW173625, AI802924, AI263005, AI286190, AA694076, AW168835, AA699535, AA625080, AI912832, AA854042, AA320461, AA704943, AI762162, AA740929, AI700148, AI241269, AA330308, AI640185, AC006359, AL021920, and AC004455.
HNHFR04	45	646709	
HOSFT61	46	862050	AI768188, AI935495, AI819745, AI422744, AI423415, AI140447, AI969550, AI332649, AI942442, AA127755, AI075724, AI199841, AI422431, AI129261, AI140453, AI050878, AI419482, AI766108, AI080121, AI675245, AI280479, AI809228, AI372882, AI335707, AI423608, AA678475, AA807943, AI221599, N79574, AA449772, AI375330, AI094106, AA987838, R44044, AW274423, AI914896, R41865, R55755, AA831552, N51677, H23272, AI014757, AW444813, R26737, AW089977, Z38205, AI540756, AA029258, T24879, R26969, AP000118, AP000165, AP000315, and AC016831.
HBUIO81	47	625977	AW301022, AA748554, and AA761415.
HADCL55	48	686761	AI891111, AW273154, AI421861, AI937106, AA844641, AI435050, AW080343, AI903718, AA010290, AW363110, AI963329, AA460436, AA460435, C18387, AA010291, W26232, N20813, H09922, AI862319, AW363122, AI131459, AI422844, AA926645, AI671988, C01597, H22803, AI147703, AA017133, Z42698, H58948, AW295951, F05928, H09826, R92329, AA156440, M78768,



HAIBO81	49	695698	AA824261, AA995248, Z38858, AA812976, AA092371, AL136827, and AB023199. AI061313, AL046519, AI733856, AA805848, AI609972, AA469327, AI753113, AI291439, AI537995, AI130709, AI687343, AW021154, AI814682, AW302659, AW302705, AI536858, AA829036, AL041375, AA829044, AW148775, T71936, AI815210, AL020997, AC002425, AC006011, AC004975, Z82214, AP000510, AC005919, AC005225, AC008033, AC004020, AL021707, AC005209, AC003110, AL133163, AC000533, AC005288, AC005529, AC006530, Z98751, AL035407, AC007226, AC005484, AL049759, AC007666, AL024474, AC007055, Z97876, AP000552, AC002470, AC007036, AC008372, AL031295, AC005261, AC006312, AC005514, AC009247, AP000514, AC007686, AC003080, AC006139, AC004655, AC006130, AC005952, AC006241, AC002369, AL109627, AF038458, U91323, AC002544, AC005231, AL049229, Z83840, AC005015, AC004408, AL078463, M89651, M30688, AL035071, AL031767, AC005088, AL118516, AC006023, AC004491, AC006511, AP000557, AC005696, AL049766, AC005363, AL035413, AC002996, AF050154, AC007536, AC005726, Z96074, AC005280, AL049569, AC004156, AL031283, Z83826, AC005060, X54486, AC005324, AD000092, AC006942, AC005251, AC007371, AL031293, AL008725, AC005049, AL031428, Z84466, Z93023, AC003669, AC004024, AC004707, AL021453, AL031577, AF030453, AP000692, AL021546, AP000350, AP000260, AB014078, AC005067, AL031670, AP000116, AC006050, AC004099, AC007207, AL133353, AC007685, AL031311, AC004878, AB023049, AC005069, Z82976, AC007637, AP000049, AC005534, AC003101, AC005519, U78027, AF001548, AC002504, AC004771, AC004477, AL035587, AC005520, AC009516, AC006487, AF165926, AL031584, AC002039, AC003982, AC005759, AC005736, AC007690, AL049699, AP000555, AC004000, L78810, AC005837, AC005409, AP000563, AB001523, AC007938, AC005488, AC005578, AP000311, AP000036, AF196779, AL050318, AC005355, AC006480, AC005954, AC004228, AC005089, AP000215, AC005694, AC007227, AP000117, AL022311, AP000558, AC002314, AC005940, AC005940, AL024498, AL035249, AC005207, AL109984, AL022323, AP000210, AC003043, AL109801, AL109758, AC007193, Z95331, AC006101, AC005912, AJ011930, AC005046, AC005971, AF129077, AC002404, AL049539, AF165147, AL022302, AC004770, AC004796, AC007731, U63721, AL049780, AC006441, AL031846, AC002400, AC005500, AL049538, AC009731, AL049839, AL023575, AC004216, AP000344, AL031659, AL022316, AL031985, AC002429, AB014079, AL121658, AC005200, U52112, AL022336, AC004150, AL035422, AL049694, U91326, AC006597, AL121653, AP000337, AF053356, AL132718, AL031597, and AC002549.
HBBBC37	50	695702	AI953024, AI570581, AI052251, AW072845, AI283137, AW418961, AI276972, AI765673, AA443232, AI218363, H98529, AI819979, AA284497, AI187773, W31829, AA971941, H19433, AI674860, AI359631, AA443194, AA857996, AA975354, AW022944, AI032489, R59463, C02118, H23263, AA776510, R60979, Z38831, AA102625, N28938, D51172, T34946, R59403, AA953086, N81166, AI823922, T90503, R45520, AA872986, R45152, W04580, AI277164, R20541, H97160, AI560504, N22268, Z19348, AA287201, M62100, R44572, AA094604, R11284, Z42669, and AB032961.
HBIMX85	51	692971	AI673085, AA716494, AW151554, AW445050, AA807345, AA926684, AI989351, AW071081, AI687590, AI523580, AW451331, AW075954, AI131215, AI333008, AA974138, AW291257, AA769392, T84096, H91806, AA765936, AW451758, C04782, AW402336, AI473525, AW028312, AA814453, AI568709, T78707, AI801411, AW085753, AW085750, AA471314, AA831522, and AL096808.
HCEES66	52	694592	AI650353, AW129672, AI564414, AI805921, N51082, AI239923, H52585, H22566, AA007234, AI241833, R42536, H52176, H24419, and N54208.
HCEMP62	53	684780	AI688113, AI554392, AA911109, AW173438, AW382483, AA486370, AA778384, AI382028, AA776265, AA563686, AI493765, AI523553, AA484857, AI362311, AA811238, AA906681, AA838288, AA460659, AI276177, AW404956, AA479791, AA259052, AI097482, AI082243, AA488079, AA088205, AI609703, AI093069, AW438882, AW366250, AA477188, AI350871, AI953839, AI033274, AA285058, AA648139, AI087234, AA226399, AA594766, H53631, H04050, AI298774, H03363, T86181, AI687929, AI270613, H48473, AA496296, H53672, H70534, AI433271, R99170, AW188898, AA359247, AA374856, R23345, H28080, R70772, R33920, AI500391, AA852639, R81465, AA297085, T83919, AA428830, R33033, AA297469, AW088943, AA621048, AI400220, AA853069, R81663,

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HE2FB90	54	691077	<p>AI857437, AI857436, AI278048, AA507045, AW273440, AW297803, AA493364, R47896, AI292326, AI364487, N66632, N58844, AI361304, AA347485, AA357233, N80769, AI374919, H08044, R47895, AW189621, AW439143, AA887910, AI394536, AI591191, AI279880, AI280275, W65494, AI797532, AA357422, H07938, W65483, and AI123607.</p>
HTHDJ94	55	693652	

			AA902128, AW027880, AA570689, AI312759, AA976250, AI092605, AA558902, AA151226, AI041784, AW262597, AA280806, N36166, W32108, AA151227, AA406299, AI090180, AA781961, AA115004, AI623995, AW239455, AI027447, AA065116, AI377228, N59607, AA451762, AI804317, AA724950, AA449952, AA450034, AA115005, AI186329, H10448, AA482977, AI242335, AA453022, AI032607, AI804465, AA640751, CI16610, AI149260, AA987598, AA781332, AI804069, AA973798, AA452663, AA127134, AA872873, H82385, T86790, T82258, H10449, F30722, T78950, W32213, AI424359, AA338139, AA296988, T78898, AI285049, AI278719, AA451764, W47452, AA541483, F06459, Z28571, Z39388, AA297494, T86695, AI318411, F01234, AA808781, AA297421, AI991656, AA661544, D31389, AA280856, AA280942, AA064799, Z24822, AA031579, AA298704, AI670708, AW238447, AA494107, AA296942, AA031458, AA297411, AA297354, AA099261, AA098866, T83540, AA297420, AI675090, AI194682, AA368017, AA297201, D20890, AI908416, AA897425, AA530981, AA411374, H70649, AA449811, F24096, AF125533, AF169481, and AF091084.
HTOHJ89	56	695763	AA101269, AI792578, AI054419, AA847499, AW023111, AI612070, AA477503, AI611533, AI379719, AI440117, AW162288, AC002310, Z97196, AL022165, AC002470, AF129756, AC004139, AC006064, AF031078, AC006509, AL022320, Y14768, AF030876, AC005088, AL022336, AF024533, AL109801, AC007308, AL132712, AL022326, AL022316, AL031255, AL031577, AL034549, AC004221, AL009181, AL022327, AC006241, AP000045, AP000113, AP000501, AP000356, AC004622, AF111168, AC006965, AC005280, AC004216, AC005702, AC005969, AC004812, AL121754, AP000302, AL032821, AC004408, AC004382, I34294, AL121655, AC0009946, AD000092, U91326, AL031677, AC007227, AC002350, AC005694, AB023048, AC009516, AL031767, AC005837, AC008372, AC005730, AC003006, AC003042, AC006011, AL024498, AL035249, AP000114, AP000046, AC007226, AC004476, AC007151, AC005829, AL031775, AC007182, Z95116, AC005911, Z95115, AF196779, AC006130, Z83826, AL050341, AC007766, AC005370, Z85986, AC002133, AC009542, AC002364, U85195, AC005231, AC006511, AC007685, AC005379, AL050318, U95742, AE000658, AC009247, AC004967, AP000555, AC005484, AP000252, AC004890, AF106918, AC007686, AP000143, AC007240, AC007216, AF165926, AL080243, AP000500, AC005726, AL049758, AC005914, AC002365, AC009330, AL031650, AC005071, AL021546, AC004381, AL008735, AC020663, AF196969, AC005067, AL049692, AL049748, AC007546, U91322, AL109798, AC007371, AC006449, Z94044, AP000354, AC004805, AC000134, AC007774, AC005212, AL035659, AC002544, AC005261, AC007367, AP000115, Z98946, AC005545, Z98742, AL031602, Z85987, Z86090, L44140, AC005933, AL049776, Z93017, AC005562, AC006101, Z98051, AL022311, AC004195, AC006538, AL022476, Z84487, AL035587, AC006938, AP000090, AC005527, and AC004780.
HUSHB62	57	680495	AI096616, AI937128, AA478989, AW148649, AI635678, AA580461, AI871452, D61293, AA701343, AA947641, AI077699, AA587392, N92014, N22807, AW090032, AI913164, AI566329, AI304741, AI832816, AI920824, AI688989, AA505810, AI474080, AI591133, AW024245, AI423395, AA918351, AI285282, AA834943, AI870350, AI559195, AA838061, AA775249, AI435008, AA703175, R97195, AI421979, AA723388, N63869, AI339068, AA478599, T16357, AA868966, AI272181, AL039420, AA769928, H28566, AA363734, AA916277, AW337191, AI262344, D81371, H19664, AI239934, R56668, H03426, AI282295, H13067, AW276930, AI197924, AW363835, R21517, AI863591, AA299531, AI001889, AI420251, R53825, AA384624, AA962591, AL121415, CI7798, AI276296, AA534355, AA013482, AA507743, Z45873, AI193397, R76057, AA947445, D78950, H53668, AI803908, R56831, AA327530, R21620, AA304103, AA327544, AI631817, F09191, AI695253, H11336, T16635, H53629, T35087, AI610263, AW275794, R12800, AI601236, R97196, AI287902, AW128986, H04135, AA574194, AW118490, Z41505, AA865671, AW192504, AW151452, AI205173, AI244106, AA477926, AW316864, AA322273, R39499, R39500, F11529, T35056, AL039419, AA960860, R75882, T19229, AW376282, AI934081, AA557576, T06706, H28565, R19084, AW384792, AJ011001, AL137591, AF106858, and AF166382.
H5XAG02	58	667848	AW370368, AW137077, AI601240, AI803696, AI168184, AA121075, AA527028, AI334348, AA603723, AI432655, AW296548, AA420755, AI371852, N28275, AI268286, H93203, AW300705, AW453008, AA420796, T09453, AI761383, AA555003, AA122417, AI864017, AI698470, T09015, F11705, AA987938, AW083439, AA826633, AA972661, AW149398, C00601, AW183138, AI828119,

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HHTLH52	59	665722	<p>AI805189, AW136027, A1634613, AA292087, A1201246, A1693706, A1675765, AW390785, AA868564, A1654869, AW390814, A1077669, AW082330, A1695580, AA995665, AA758454, AW373785, AA757902, AC004893, AL133396, AF165142, AL034374, AC004837, AC002416, AP000045, AP000113, L44140, AC006501, AC003071, AC006255, AC005058, AL096776, AC008014, AC002326, AC005663, AC004797, AL049795, U95739, AC004878, AL031721, AC005488, AC005291, AP000116, AC007193, AC004084, AL009031, AF199364, AL022165, AL031390, AF030453, AL035450, AC002301, AL022163, AC005088, AC005224, AC004966, AC006210, AL049553, AC005520, AC011311, AC005216, AC002527, AP000013, AC004477, AF001549, AF045555, AC007425, AC004613, AL022315, AC016027, AC004213, U95742, AL121603, AC007216, AC002558, AC007358, AC005971, AC006312, AC003666, AL033521, AC005562, AC005519, L78753, AC005081, AL021329, AC002394, AC007773, AC005028, Z84486, AC007245, AP000226, Z83838, AP000250, Z98036, AL031282, AL031283, AP000087, AC005962, AC002565, AC004884, AL022723, AC003089, AC000119, AC005157, AC002086, AC005250, AC002432, U51560, AL079342, AC005102, AC007055, AL109865, Z84480, AP000211, AP000133, AP000030, AC004139, AP000344, AC002377, Z80896, AC003108, AC005242, AC002365, AC006120, Z93930, AC006344, AL035072, AC002430, AF064865, AC009113, AF111168, AL133445, AC003111, AC005074, AC002289, AC007384, AC004134, AL021937, AC006203, AC004895, AC006112, Z82214, U91323, U62317, AC005479, Z99297, Z93244, AF067844, AC006139, AC008372, AC004465, AL031774, AL021393,</p>

HCfMS95	60	674464	<p>AC007151, AC005993, AC003029, AF088219, AP000359, AC009320, AC007237, AL022721, AC002504, and AC000025.</p> <p>AW276842, AL036382, AI963720, AI637587, AI954260, AI708009, AA610491, AA581903, AW439558, AI633390, AI859284, AW193265, AW085780, AI345654, AW082108, AA491814, AI956144, AI831819, AA569471, AL046409, AA493471, AA623002, AW304584, AA526979, AI344844, AI564454, AL042420, AI061334, AW088846, AI177120, AI284640, AI064952, AI814735, AI890570, AI890928, AI561060, AI568678, AL119691, AW265393, AI860020, AL121385, AI273968, AI783494, AA714453, AA828042, AW303196, AW274349, AI355206, AA551552, AI431303, AI670124, AI345681, AW301350, AI345675, AA578861, AI801600, AI956131, RG6997, AI350211, AW070892, AI305766, AW238278, AA947364, AW088202, AW083402, AI613280, AI270117, AA601492, AW276827, AA598824, AA371434, AL041690, AA806796, AI368745, AW303876, AW119262, AI141675, AA594725, AA683258, AW083364, AW250970, AI446464, AA226153, AW438643, AW302013, AI807650, AA535661, AA225246, AI239488, AI085719, AW189303, AI619997, AI064864, AI281881, AA559290, AI334443, AI136338, AI634384, F36273, AW265009, AA469451, AA483223, AA219129, AL040130, AI873916, AW102955, AA781975, AI669453, AA525898, AL037683, AW082492, AA507824, AA468131, AI368256, AA643962, AA678671, AA775230, AI471481, AI431240, AA525790, AA632994, AA079831, AI623898, AA809029, AI110688, N54894, AI625244, AI561255, AW249224, AI754658, AL048925, AI345157, AI053790, AA526787, AW270619, AW104748, AI374809, AA503475, AI375710, AA649642, H71429, AI133164, AA526191, AW151855, AI889923, AA513141, AW276435, AW193432, D82290, AI688846, AW088718, AI160117, W79504, AI969436, AI538433, AA513181, AW029038, AL044940, AA570227, AI908381, AI240168, AA468022, AA584881, AI537955, TS3128, AI801591, AA523837, AI798473, AW085794, AA552856, N53150, AW410400, AI251436, AA583955, W47183, AA877817, AA531372, AA720702, AW162049, AA652057, AI962050, AI929531, AA280632, AL138265, AA493206, AA857486, AW261871, AI859742, AI610159, AI689222, AA665021, AI636627, AI370094, AI345518, AW162246, AA908422, AI635818, AW088224, AW270382, AI370074, AW265385, AI798266, AI312309, AL022316, AC005031, U80017, AC004999, AF084195, AC005773, AL031055, AL079340, Z82217, AC007993, U85195, AE000658, AP000082, AC019014, U57004, AL031429, AL034412, AC005480, AC005264, AC008078, AL117471, U57007, AC004234, U73479, AC006392, AJ251973, AC006059, AF015155, AC004087, M94634, Z93017, U01102, S75201, AL033375, AL021938, AC007382, AC004941, AC004010, AF015153, AF015148, AL009029, AL049844, AC006238, Z98043, AF184110, X51956, AL022156, Z97987, U47924, AC006292, AC006276, U57009, AC006512, AF181449, AL031577, AB028893, AC004098, AC004009, AC002449, X74558, AC004870, D83989, AC005221, AL022476, AP000305, AC006449, AC005250, M19364, AP000047, AC005815, AL031293, AL049761, U18391, U18392, U57005, X55925, AF0118497, Z83844, X69951, U38672, AC007151, U18394, AC006077, AC006126, AC006057, AP000115, X53550, AF015157, AC005323, AF077058, Z82198, AL035659, AC007068, AL031255, AL133353, X54181, AC005391, AC005548, AL022302, AC005162, X54180, U18398, U57006, U18395, U18393, U57008, AL034562, AL023553, X54178, AC007671, U18387, U40369, X75335, AF076952, AF156539, X55926, U18396, Z95124, AC003695, AC004853, AL136295, X54175, X54176, AC006536, I51997, U18400, AF050154, AF144630, AL078581, AL121603, AF064863, AC003081, X55931, AC004745, AP000348, AL022322, AL096678, U18390, AL109865, AL078474, X55924, AC004594, AL121934, AL133396, AC005599, AC006539, AF015151, AL117344, AC005696, AC005919, AC005261, AC007537, AC005076, U18399, AC005154, AC006041, AC005210, AF045448, AL023807, AC004047, AC004501, AC006367, AC005518, AP000359, AF121781, AF088219, AC006130, U62317, AC007065, AC007681, AC007564, AF015147, AF015156, AC005682, AC007103, AC002508, AC004019, AL031313, AC006312, AC003050, X54179, AL023803, AP001137, AC006989, AF196779, AL035681, AC006597, Z98751, AC004894, AL031315, X55932, L81583, AF085442, X55922, AL049631, AC002470, AF015152, AC008249, AC006537, AC004895, Z98200, AC004672, AC005690, AC007676, AF015154, AP001172, Z98744, AC002564, AF190465, AL031585, AC006120, AC005701, M37551, U67801, Z82245, AC000115, AC007324, AL008732, AL035695, AC008101, AC007043, AC006213, AF031077, AL049709, AF135028, AC005084, AF015167, AC005324, AF117829, AL078604, Z97632, AL050308, AL031446, AL136504, AC008079, AP000567, AC005304, AF015158, AC003957, AC005102, AL031668, AL022323, AP000356, AF074708, AC002368, AC007371, AC007656, and</p>
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HOUCT90	61	646817	<p>L48038.</p> <p>AW023515, AA715814, AA659232, AA513851, AA704393, AW237905, A1753672, T05118, AA602906, A1683131, AA535216, A1307201, AA019973, AW327422, A1076228, AA559241, AW023975, A1267269, A1635440, AA410788, A1249365, A1380617, AW023111, A1523316, AA644090, AA683069, AA654778, AA668291, A1144081, AA569591, AW062682, A1923052, A1792521, AA169245, AW302711, AW304580, A1056177, AA633892, A1365625, A1929410, A1792499, AA640430, AA630535, AA492015, AA515048, AA182731, A1887235, AA115863, A1912401, AA470567, AA455483, AA484267, A1246796, A1079734, AA659832, AA825827, A1053793, A1049709, AW316599, AA747757, A1669421, AA572813, AA084609, AA487272, A1754170, A1192440, AA669238, A1038842, AA583394, N35306, AA515728, W96277, AW270619, AA640410, H78898, A1053934, AW407632, N23913, AA780515, R95840, A1037714, A1874201, A1538491, A1628859, A1675615, AW410354, N34477, AA502532, AA313025, N72170, AA503298, AA282820, A1224619, AA622801, AA714011, A1362442, AC004876, Y07848, AC000026, AB023050, AC002059, AP000511, AL022238, U89335, AC006992, AC007021, AC006549, Z85987, AC002511, AL049776, AC006441, AC007663, AC006430, AL050332, Z85996, AL031281, AC003950, AC004686, AF031078, AC005104, AL109798, AF030876, U95742, AP000558, AC009516, AL031685, AC018633, AC006130, U07562, AC005058, AD001527, AC007688, Z95116, AP000047, AL021394, Z82176, AC000070, AC004707, AC000082, AC004408, AC006064, AP000115, AL121655, AL022336, AC004794, A1246003, AC006312, AC006547, AC005390, AP000553, AL049872, AF134726, AC007684, AC005482, AP000304, AC004851, AC005081, AC002504, AL049745, AP000302, AC007216, L78833, AC002302, AC004382, AC000097, AC004814, AC004067, AC004032, AC004991, AC006468, AC005071, AL034548, AL049757, Y10196, Z73359, AF222686, AL049538, AC005180, L44140, AC005908, AP000141, AP000143, AC007151, AL031666, AL031588, AC006077, Z84469, AC004079, Z93024, AC004212, AC000393, AC004106, Z97184, AP001060, AC005284, AP000694, AC004638, AJ009610, AF042090, Z82215, AC003042, AC005829, AC005138, X58050, AC004671, AC006543, AC005041, AC005800, U78027, AC002404, AC005412, AC004057, AL031664, AC003109, AC005324, AC005529, AC005183, AC007731, AC004694, AL031282, AL035413, AF111168, AC006080, AC004655, AL035422, AC002350, AL109758, AL023284, AC004882, AC005212, AC007899, AC004531, AC006211, AL035417, AF196969, AC005005, AC004783, Z98044, AC004019, AF109907, AP000114, AP000046, AC007546, AL021940, AC007540, AL021707, AP000152, Z92542, AC005695, AC005031, AL022165, AC004878, AC005043, AL022237, AC006011, AP000557, AL079342, AB004907, AL022316, AC005046, AL133163, AF050154, AC002310, AC002394, AC006544, U80017, AF031076, AC000025, AP000505, AL020997, AP000279, AL109801, AL035658, AC002365, AF001549, AC004945, AC005952, AL031005, AC008038, AC009247, AC007386, X55922, AL035659, Z98036, AL031427, AC004834, AC007537, AC008040, AL008715, AC004678, AP000512, AL021391, AC007868, D87675, AL021546, AC003065, AC006449, AC005500, AC005527, AL031589, AC005033, AL031659, AC005765, AL133448, AC004955, Y14768, AP000501, AC002476, AC002984, AC002425, Z73360, AL023807, Z81365, AC004887, AL133500, AC006930, AL022302, AC010205, AC003972, AF129756, AC007156, AC005409, AL035461, AC005667, AC004033, AC000090, Z93241, AC000159, AC005015, AC007051, AL109984, and AC003983.</p>
HCFLR78	62	679532	<p>AA573144, AA005018, A1978717, A1983151, AA007460, AW129961, A1023529, A1023528, A1097101, A1138990, AA429301, A1307122, A1281472, AA724365, AA074611, W47513, A1126957, AA843528, AA621024, N92125, A1151489, AA005019, A1023888, A1963099, W74039, AW296547, W47514, A1052664, A1369723, A1470114, AA203390, AA634442, A1289000, H75708, A1288995, A1131387, A1093686, H77802, AA470883, H09852, A1092232, AA758859, AA873611, AA463447, AA663901, AA365043, A1080292, H12975, AA937147, H17224, A1014968, R74259, AA612948, AA682858, AA609107, AA358497, AW009774, AW383643, AA443488, A1076595, A1243243, AA426125, AA862640, T99925, A1636974, A1363306, A1246182, A1050921, AA508211, D55400, AW445069, W19308, AA865885, H66722, N77454, A1266464, A1018497, R02421, AA889290, A1247759, H75637, H00584, H00583, R28482, D53939, A1798308, A1909657, R09589, AA449327, W72360, W90696, R32666, AA873850, AA074610, AW264053, AA524719, N63685, AA515478, A1742730, AA425024, F29136, AA429478, AA843783, AA635518, A1263801, D52605, AW008958, and AF151807.</p>

HTOHT18	63	628300	and AC004928.
HKPMB11	64	688048	AI767027, AI985304, AA552150, AW058459, AI762127, and AW363648.
HNFHS38	65	872798	AA576409, R33161, AL036490, AF064782, I89937, and I89938.
HAIBU10	66	695699	AI767136, AW003744, AA553744, AI360184, AI565814, AW051486, AA505513, AW301029, AA679066, AI376801, AI341735, AI268928, AI761796, AI090327, AI767627, AI700593, AI538258, AA987212, AW003752, AI185049, AI682919, AA460766, AI343947, AI174548, R72610, AW027615, AA460166, C01651, R68273, R72274, AW207668, W46139, AA329290, AI393145, AI624837, AA810925, R11148, R94606, T84462, AI749190, AI659411, AI757401, R11149, AI424444, AI635008, AI337023, AI539289, AI7173060, AA961062, AI150522, AA535727, AI797658, AW304422, AI620080, AA609486, AI911307, AW269588, AI357832, AI762382, AA723777, AW449936, AI937537, AI699787, AW235819, AI806859, AW182752, T96516, AA039581, AA993113, AI7196492, AA931719, AA749267, AW003753, AA938372, N87192, AI750035, AW074390, AI239833, AI979278, AA722791, R68308, N95006, R94246, R97183, AA385572, AA811736, AA090761, AW294034, AI675733, R29264, AI628714, AW418794, AI700162, AI418602, AA905467, AW362416, and A W362436.
HAPOK30	67	685705	AI350913, AA456130, AA459754, AA9222659, AA729889, AA897044, AW207589, R60787, AA373089, AA514352, AI797424, AA737686, AI434406, AI025403, AW295994, AI492263, AA811057, AA629548, AI823834, AW027718, AI741138, AI637804, AI521795, AI094328, AI420179, AI277236, N26754, T16381, AW271660, AW337972, N66648, AI242353, AI094233, AI042022, AI690072, AI273673, AL036251, AA487475, AC004659, AF126403, AC005184, AC001231, AE000658, AC007564, U85195, AC005829, AC007227, AC007934, AL049775, AL109938, AL035079, AC005377, AC005250, AC002070, AC011504, Z83821, AL020991, AC006313, AP000514, AB014080, and Z99128.
HCEEM18	68	694615	AI433694, AI287242, AA016140, AA769504, AA248824, AI174876, and AL031230.
HCWUA22	69	695683	
HDSAG91	70	692361	AL048773, AA837369, AA056206, AI200051, AW265393, F32668, AW023111, AA657918, AI307201, AA484148, AI815425, AL046746, AI267349, AW269488, R96401, H98660, AI349874, AW438542, AA664521, AA218851, AI264743, AI267450, AI267847, AW021116, AI623720, R90740, AI267356, AI499503, AI287832, AW028429, AA664604, H73070, AW270768, AW277174, AL045848, AA693370, AA713570, AA604843, AA167744, AI538852, AA713569, AA826144, AL118947, AA317170, AA381762, AA651864, AA584581, AI921188, AA577852, AI801482, AI446205, AA714595, AA877817, AL133243, AC008015, AP000046, AC006960, AC005215, AL031276, AL023284, AC005228, AL033527, AL022162, AC005091, AC002504, AC007191, U82695, U76377, AL035458, AC007539, AC002364, AC007130, AL049872, AL117351, AC004549, AC006061, AL034345, Z97205, AC006487, AC002543, AL078581, AP000338, AC007172, AP000216, AC006455, AC004531, AL031228, AC008282, AL031652, AC012384, AL109628, Z82243, AF107045, AC006344, AC004381, AC004087, AL117355, AL023694, AC005516, AC007216, AP000090, Z95118, Z84487, AL117258, AC004712, AC005161, AC004982, AL049569, AC002302, AC007030, Z74739, AC007057, AC005829, AC007347, AC004217, AF015416, AC004975, AC002105, AL049761, AC003957, AF196971, AL139165, AB022337, AL024508, AL049563, D87675, Z93931, Z98751, AC006088, AC004900, AL049552, AC004858, AL035361, Z82184, AC000118, AC005669, AL021328, AL021937, AC004894, AC002454, AC007102, AL121694, AF109907, AC005249, AL122003, AC007551, AC007314, AC002457, AR036572, AL078462, AC006101, U91328, AC007970, AL122023, AL022726, Z73358, AL049697, AC005075, AL031668, AJ010770, AC005005, AL109613, AC016025, AL022401, AC004848, AL050308, X54175, AC004702, AC007656, AF067844, AC007114, AC004013, Z95113, AL035454, AC006285, AC008040, AF165926, AF114156, AP000965, AC005154, AC013417, AL121769, AC018633, AL031255, AC002476, AC006084, AC004703, AL078474, AC005902, AP000011, AC004638, AP000030, AF104455, AL021453, AC002531, Z93016, AC005722, AC004128, AP000211, AP000133, AP000884, AC005011, AL049835, Z93244, AC005288, AC007676, AL031283, AC006115, AC002331, AL022723, AL121658,



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HNEDJ35	71	695744	AI613459, AI090377, N68677, AW275432, AI310670, AI224583, AA573067, AI016704, AW085751, AW410844, AW151102, AI124798, AA489390, AA595661, AW021917, AW080811, AI547110, AI654285, AA809125, AI334435, AA013168, AL121039, AI433952, AI702049, AI284583, AL037910, AW272815, AW075979, AA365586, R23873, AA324108, AA019973, AW117740, AA831426, AA425283, AA350886, AI174703, AA693484, AW148821, AW151247, AA904275, AI753131, AI251696, AI523205, AI355572, AW265468, AW327868, AI349130, AI049999, AI690379, AI935827, AA904137, AI926728, AA631915, AL037067, AW327624, AI078409, AI473671, AI061313, AW270652, AA484143, AL041375, AA629992, AW270258, H07953, AW302659, AA743996, AW302705, AA584360, AL045709, AA828045, AW265385, AI921161, T74524, AA602906, AW302315, AI801563, AA525423, AL079734, AA311535, AL039117, AA640305, AA720732, AI439525, AA679946, AA280886, AI754037, AA720582, AI887468, H62123, AI452836, N99245, AA507623, AI445815, AW327852, AA642809, AI754421, AW167799, AA878149, Z49154, AC007207, AC005386, AL080243, AC007541, AC005516, AC002558, AL022328, AC006132, AL117340, AL049869, Z83826, AC005993, AC006271, AC016027, AC002302, AL132641, U95742, AC005004, AC004253, AF038458, AC007216, AC007421, AC002314, AC002430, AL035072, AC007384, AC005488, AC000052, AC005081, AL021707, AC016830, AL022320, AC006251, AC004150, AC006543, AC004000, AP000111, AP000043, AC008044, AC002563, AL021978, AC006285, Z98200, AC003101, AC005632, AC003035, AL031848, AC004820, AC005668, AC005531, AL049776, AF205588, AC006544, AL021453, AL133246, AC004019, AL034420, AC006449, AF045555, AP000326, AC007676, AL050343, AC006236, AL133243, AC005940, AP000169, AP000122, AP000054, AP000359, AL078581, AC012331, AL049760, AL096791, AC005288, AC005527, U80460, AC005060, AC007395, AC008082, AC005247, AP000688, AL049694, AL031587, AL050348, AC003029, AC002347, Z83856, AC008101, AL121754, AL133448, AC005971, AC004560, AC005234, AC004796, AC005696, AL049589, AC000085, AC005529, AP000557, AC002425, AL117258, AL121653, AJ003147, AL117337, AB023050, Z95152, Z92543, AC005703, AL035414, AL049570, AL008582, AC005057, AL022316, AC004771, AL136295, U85195, AC004893, AC005694, AC002044, AF207550, Z98256, AC003042, AE000658, AL049794, AC005502, AC004050, AC000025, AF109907, Y18000, AL031427, AC006137, AL121658, AL117694, AC005899, AC006126, AC005291, AC005225, AL049766, AC005218, AC008079, AL121603, AC007204, AC007308, AC006347, AC004079, AC005837, AC007151, AC004087, AC004590, AF134726, AC006241, AC005841, AC006120, AC006013, AP000509, AP000009, AI011930, AC003982, AL049758, Z84480, Z94056, AC004678, AC004212, AC002395, U91324, AC005856, AC007731, AC004686, AC007666, AP000248, AC005500, AC005553, AL022326, AC005921, U91321, AP000692, AC007298, AP000552, AC008009, AC005800, D84394, AP000556, AL031255, AP000512, AP000354, Z75887, AL035696, AC005519, AL109985, AP000301, AC002428, AC003043, AC005399, AC002091, AC004878, AC002470, AC004895, AL034549, AC005832, AC004821, AC005046, AL049576, AL096701, AC005257, AL121655, AL109963, Z83840, AC005091, AC007845, U73023, AC006373, AC007537, AC005255, AF196779, AC003665, AC006160, AC003070, AL049780, AD000812, AC005300, AC007055, AL049757, AL031650, U62293, AC002300, AC004975, AC002312, AP000080, AL021391, AC007041, AL049778, AE000659, AL031588, AC005284, AL035415, AC005003, AC002301, AC006480, AC006441, AC004020, AF196970, AC007225, AC005231, AL033527, AC005220, and AD000092.
H77BA62	72	861995	R82515, AA514191, AA514190, AF121051, AF095853, AF033115, AF018071, D44443, L39119, AR038762, AJ005168, Y11107, AF046029, U67221, AJ245869, AC005501, I58669, I15353, AR018866, U89924, A58521, AB029348, D88984, AF054142, A49700, U85943, AF033196, AF095855, I65436, AR062871, D49729, AJ001044, AJ006789, AF013625, AF044960, AJ250192, U92795, AF019721,



			and AF045229.
HNGIO50	73	691288	
HMIW81	74	667504	AA614239, and AC006518.
HMMCJ60	75	663467	AL118912, U91321, and AC003982.
HDPIO09	76	686765	AI804463, N22803, AW373516, N32577, AW182870, AA676790, W87853, AI038081, AA478157, AI334288, AA776795, AA306403, AI351376, AI203592, AA280706, AI089377, AW205251, AW391127, AI675872, AW391220, N30775, AI123770, AI148454, AI222245, AA133659, W90305, AI220222, W87683, AA418887, AI472099, AA133660, R13704, AA127057, AW367495, AA932329, AA287753, AA948045, H04073, AA826530, AI266054, AA742688, W90615, AI024654, AW408660, AI184331, AA255740, AA025466, AA418888, AI094116, AA431370, AW391079, AA343934, AA456495, AA545796, R81593, AA419218, AI191834, AI2755548, AA001310, H69110, AA432367, AA255539, AA680159, AI218857, AW166628, AL120413, AI468727, AW102705, AA203443, AA384514, AI740920, AA846384, AA001680, AA478158, AI417822, AI863025, AW383212, AW205723, AW374902, T98259, AA361259, AA001638, AW166981, AL121099, T98314, AA360747, AI148591, R27882, R18829, AA476304, AA125934, AW390975, AA361382, AA013465, AW391073, AA767404, AA262028, T25723, AA832312, C21543, AA373327, AA419219, R81340, H03380, AA993124, AW139299, AA628282, and AB007963.
HHFHH34	77	688045	AL109984, AC007216, AC004228, U95742, AL049759, AC004770, AC005694, U95090, AB023048, AP000694, AC004883, AC0077238, AL022238, AC006536, AL031053, and AC006947.
HISCL83	78	688047	
HTOAI70	79	840223	AI002744, AA636025, AA838190, AI223700, AC004049, AC004408, AC006511, AC006212, AC005747, AC002565, AC007066, AC005736, AL031311, AC004032, AL133448, AL096703, AL034417, AC004967, AC005071, AC006013, AC003101, Z85987, AC002492, AC007546, AC005191, AC002554, AL035423, AF001550, AC000029, AL022323, AC006101, AL035400, AC000353, AC005914, AL022336, AL121653, AF111169, AC008134, AC002351, AC004832, AP000696, AC005682, AC006449, AC004067, AL050307, AF038458, Z82194, U91321, AC006946, AC008072, AC007842, AL132985, AL031985, AC005280, U52112, AC005189, AC007227, AC005384, AC004976, AL008718, AP000248, AC004216, AC004526, AC016026, AC005486, AC005512, AF176915, AL035249, AC006139, AP000514, AC004531, AC005181, AL031283, AC004703, Z98304, AC007021, AL035420, AC003661, AF001549, AC004491, AC006960, AC007461, AL020997, AC000105, AC010582, AC004112, AC002551, AC010197, AC006006, AC005015, Z98950, AC005229, AC009263, AC005562, AC006973, AC004815, AC005880, AC005043, Z97054, AC005207, AP000100, AL096791, AP000688, AL034548, AC006568, AC005666, AL121655, AC004770, AF003529, AC005722, AC005608, AC007327, AC009464, AL022165, AC006991, U96629, AC005031, AC003663, Z85996, AC002543, AC005255, AC005081, U91327, AC004099, U95626, AC004887, AC004520, AC004905, AC005300, AC004707, AC006084, AL035417, AC004381, AP000359, AC004841, AC002369, AC007488, AC005046, AF111168, AL121756, AC002070, AP000117, AC004876, AL122021, Z77249, AC000025, AL031721, and AC001226.
HSDER95	80	664502	AW005333, AA631227, AA143192, AA181022, AI301959, H98648, AA594850, AI478582, AA287457, AI393857, N75788, AA211849, F06608, N22567, AW450628, AA563681, AW195766, AI915322, AA186657, AA992992, AA143136, AI302352, AA631048, AI341927, AI870902, N75929, AA973384, AA160641, and AA338837.
HNECL25	81	618777	AW243793, AW022608, AW270258, AA287872, AA490908, AW304580, F00564, AA487475, AL048275, AI050070, AL042756, AA631396, AW117829, AA601278, AC000159, Z95152, AC004832, AC005089, AC005527, AC007546, AC005529, Z97054, AC005899, AC005081, AL049540, AC007227, AC006211, AL049776, AF111168, AP000030, AC004263, AI109865, Z93016, U52112, U85195, AL031602, AC004966, AE000658, Z93017, AC005519, AC007225, AL109801, AC004531, AL133448, AL049779, AC005736, AC005071, AC002126, AL022323, AF134726, AC005844, AC007666, AC004228, AL121653, AC005088, AC003665, AL133163, AC005874,

			<p>AF134471, AP000553, AC005225, AC006530, AC005049, AL035587, AC016027, AC006480, AL022313, AL020997, AL034429, AL049795, AC005944, AC005197, Y14768, AL049758, AC008072, AL022311, Z86090, AC002115, AC005484, AL096791, AC016830, AC004019, AL080243, AC002425, AP000505, AC007114, AC007934, AC007308, AC005291, AC003029, AL035659, AC005200, AF196971, AP000251, U95740, AC010197, Z98884, AL009183, AL034549, AC004821, AP000152, Z98036, AL031848, AL096701, AC006312, AC004659, AC005913, AC006241, AL035458, AC004217, AC004686, AC020663, AC005821, AF001548, AL031680, AP000503, U91323, AL022316, AC005104, AC004841, AC005668, AL021154, AL049757, AC007057, AC007371, AF030453, AC002316, AP000116, AC005670, AC007842, AF118808, AC002400, AL049713, AC005231, AC004674, AL022165, AP000350, AC004963, AL049764, AC005839, AL022320, AC009247, AL121652, Z99128, Z83846, AC015853, AC004106, AD000812, AC005632, AL121603, AC005781, AL049636, U96629, AF111169, AC002365, AL050321, AC006449, AP000351, AC005488, AC000052, AP000269, AL139054, AL031311, AC004876, AP000555, AL023284, U91318, AC003678, AC002350, AC007688, AL133445, U62317, AC005209, AC007676, AC004703, AC004922, AC004084, AF067844, AP000557, AC007637, AL031589, U62293, AL035089, AC004813, AC006441, Z93023, AC006111, AC004678, AC002483, AC002470, AP000500, AC004967, AL031846, Z85987, AC004087, AC002312, AC005778, AC005015, AC005740, AC007450, AC006057, AC007686, U47924, AC005531, AC005046, AC004962, AC002551, AC009516, AP000103, and AL022721.</p>
HNFGZ45	82	618786	<p>AI887235, AI192440, AW410784, AA282951, AA579130, AA904211, AW023111, AA579152, AA568747, T50676, AW270258, AW303098, AI250552, AI362442, AI278972, AI251284, AI284543, AA613630, AA084609, AA482776, AI251034, AW020088, AI431513, AI275982, AI366555, AI590906, AA602951, R83708, AI446452, AW029515, AI561210, AI872216, AI115863, AI821714, AI792133, AA595499, AI791913, AW189113, AI254770, AI799421, AA912287, AA225406, AA613624, AI792464, AI888468, AW303196, AW274349, AI693979, AI821785, AW272294, AA550850, AI284092, AA947265, T06518, AW079761, AW301350, AI249853, AI859946, AI272052, AI732789, AI380617, AI669421, AI635028, N22058, AC005189, AP000346, AP000347, AC004125, AL049779, AC007993, Z95115, AC006160, AC002073, Z94056, AC006088, AC003957, AC006537, AC004084, AC007151, AL023096, AL121578, AF196969, AL020997, AC007842, AC007637, AC005902, AC006064, AL117258, AC003070, AL031311, AC005703, AC002347, Z85996, AP000359, AL031597, AL034548, AL079342, AC006006, AF001552, AC005920, AC004408, AC002395, AC006312, AL132712, Z82244, AC004834, AC006965, AL022726, AC005736, AC005914, L78810, AL078463, AC006948, Z85987, AL031589, AF165926, AC004000, AC005081, AC005514, AC004982, AC004097, U89336, AC005031, AC006450, AP000302, AB023049, AF129756, AC004837, AP000115, AL132800, AL096701, AC005192, AC007425, AC007688, AL035683, AL049778, U91322, AC008170, D87011, AC010206, AC002375, AL021808, AF037338, AC008085, AL132641, AC007221, AL133355, AC002302, AL009181, AL034420, AC002554, AL035249, AL049569, AC005971, AC004520, U91319, AL009172, Z82215, AC005005, U95739, AL035587, AB003151, AC002563, AP000513, AP000114, AP000046, AL031729, AC004466, Z83844, Z93017, AC004477, AL121603, AL021707, AC006449, AL022323, Z68869, AC006050, AC005082, AC002551, AL035462, AC002352, Y10196, AC004929, AC006111, AL022163, Z82188, AF196972, Z99570, AC007242, U91323, AC002492, AC008044, AC000392, AP001049, AC004492, AC004659, AF017104, AC006487, AC005316, AC005488, AL031228, AC004525, AL031291, AL021918, AC004815, AC005231, AC005291, AL049872, Z85986, AL031659, Z86090, AC008080, AC005225, AC005837, Z97183, AC006505, AC005066, AL035361, U91318, AC002303, AC006398, AC004927, AC005988, AC004526, AP000172, AL050307, AC008249, AC004448, AC009044, AC002300, AC006040, AC004812, AL122023, AP000057, AC004778, AC005071, AL031680, AP000085, AP000694, U91327, AC005520, AC005317, AL049540, AP000125, Z98257, AC004531, AL022336, AC005666, AL049712, AL109802, L77570, U95090, AL031276, AL020995, AC005778, AL021397, AL022316, AL080278, AC005562, AC002301, AL021391, AL034412, AL031670, AC003029, AL022721, U47924, AC004876, AL034554, AF207550, AF111167, AL021155, AP000493, AF196779, AC002565, AL049759, AP000558, Z83838, AF006501, AC008018, AL031678, AP000550, AC005245, AL031984, AC004230, AL021878, AC004099, AC007160, AC004816, AC005874, AF134471, AL022476, AP000338, AC007292, AL049539, Z97195, AF099810,</p>

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	84	693214	AA610125, and AA679911.
HETDT81	85	684320	AA663075, AA047850, N58606, AA077458, AA856937, AA828871, AA807210, AA078031, AA077602, W58609, AW129389, AI186819, T87361, AI089362, AI287723, AI874364, AA450298, AA323098, AA411245, AA437334, AW105275, R50539, AI123195, AI566985, AA928290, AI418162, AA411170, AA731141, AA810894, AA812128, AA419599, AA463970, AA427583, AA862081, W58608, AA306683, AI866126, AI500451, C01071, AW058069, AW058057, AA291009, AA447967, AA001158, AA078563, AA290621, AI805526, AA015835, AI805341, AA610550, AA078595, AA393321, AA077098, R27266, R66759, AI520978, AA291720, N26141, AI571067, AI096500, AI027709, AI885893, AI225016, AI434401, AI889278, AA291823, H82512, AA635813, AA583169, AA503752, AA780801, AW089311, AI206412, AI888819, T16137, AI141818, AA035214, AA161026, AI282157, AI375694, AA282042, AA437275, AI761298, AA908680, AA411808, AA770647, AI985940, AA098984, AI500026, AI355393, AI039000, AI039733, AA917605, AA621085, AA037468, AI282159, AA077481, AC006014, AC004878, AC005488, AC005071, AC004084, AC006480, AC005088, AF030453, AC002045, AL049760, AC004656, AL049694, AC002492, AC006210, AC004998, AL023283, AC004865, AL034408, AL121576, AC005090, AL022308, AC009411, AL049828, AC005066, AP000702, AP000701, and Z95889.
	86	690808	AI823398, W27116, AI581128, AL119465, AA897785, AW004741, AI808377, AI280964, W28405, R60290, AW006936, AI872266, AW137140, AA383051, AI167420, AA215764, AI362366, AI184026, R28463, R26454, W07404, AI701315, AI871468, and AF110799.
HHLBA14 HLTBU43	86	690808	AL046937, H08012, H08129, AA309286, Z43050, R22834, and AC006924.
	87	695735	AI133350, AI739016, AW300169, N36266, AI972422, AI826155, AI678721, N28853, AA769899, T41222, T40368, AI086442, AL050309, Z69733, AC004038, AC010349, AC005062, AL121654, AC002524, AC005389, AC008109, AC009411, AC007527, AC003035, AC005250, AC006600, AL050334, AC005969, AC004025, AL031114, AL023876, AC000110, AL121578, AC004020, AC004865, AC004029, AC011422, AL049843, AL022575, AL030995, AC005145, AC003971, AC004015, AL022401, Z92846, AC002980, AC010196, AC006971, AL035552, AL136297, AC002075, AC005014, AL008708, AP000233, AP000147, AC003080, AP000152, AP000011, Z93341, AP000360, AL049834, Z99128, AC000053, Z93403, Z74696, AC002479, AL121782, AL034350, AL132800, AC004629, AC003013, AC002060, AC000004, AJ006997, AL031387, AL049875, AB014088, AC005518, L11910, AL133233, AL049830, Z95325, AC004384, AP001137, AL109620, AL031054, AP000516, AC004835, AP000526, AC007363, AC005537, Z98746, Z82203, AL031885, AL035423, AC006155, AC006367, AC004103, Z95124, AC005002, AP000069, AL122023, AC002476, and AC002448.
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HTHBH29	96	882405	AI284640, AW276435, AI610159, AI613280, AI580652, AL046409, AW276817, AA623002, AI821271, AI249997, AA488395, AA469451, AI888518, AI653636, AI963720, AA569471, AW303196, AI334443, AL041690, AI246119, AW023672, AA856954, AI814735, AI887483, AI744995, AW301350, AA610491, AA613345, AI358343, AI053790, AW270270, AW408717, AW406162, AL048925, AW406447, AA877817, AI434695, AW169537, AI357288, AW148792, AI149478, AI053672, C75026, AI589230, AI133164, AA394271, AW274349, AW338086, AI085719, AI267818, AI537955, AI499938, AA583955, AW238278, AI890348, AI431303, AA908357, AA653618, AI374809, AA244357, AI133102, AL042420, AI564185, AA493471, AL119691, AL138455, AA488746, AA577906, AA808877, AA665021, AA653975, AL037683, AI336660, AA490183, AA503475, AI830390, AA581903, AI521679, AI270559, AI286356, AW008952, AI148277, AI246796, AW071196, AL138265, AW265385, AI349850, AL044940, AA468131, AA649642, AI951889, AA758934, AI005388, AW301809, AI749559, AW265393, AL044858, AW162489, AI471481, AI951928, AA669840, AW327868, AW303876, AA708678, AL046898, AI434706, AI368256, AI564454, AI871722, AI270117, AI281903, AL046205, MT7974, AW083402, AI565581, AW088202, AI817516, AA503258, AI446601, AI307201, AA491814, AA126035, AA491284, AI298710, AA514737, AA908422, AI266576, AI669453, AI951863, AI457397, AI801591, AI471543, AA515905, AA633936, AA079462, AI061334, AW088846,

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HUSAM59	97	<p>664505</p> <p>AI097107, AW070331, AA885479, A1808635, A1808760, A1806642, A1359136, AA526850, A1743373, AA830249, A1097104, A1418914, A1263892, AI091575, A1742264, A1660637, A1218017, N25567, A1687290, A1149468, A1423504, AA036058, A1425096, AW080003, AA662766, A1699928, AW136639, A1674380, AA278628, AA789184, AW172424, H09719, A1950490, A1435913, A1092275, F34735, W31769, A1192998, AA479063, AA659932, AW003176, AL134147, AA907350, AA768824, A1968635, AA253111, W32476, AA576431, A1470700, AW303675, AW196635, H14752, A1216029, A1624069, A1005582, AA021513, A1659546, N68031, R63310, R12287, AA280617, AA158531, H13396, AA843425, A1474557, AA319692, A1087824, AA912809, R18232, R84736, AA770430, T73345, R25515, R36860, AA988334, H96095, AA868055, AA768638, AA299057, AA369839, A1762252, N52758, A1758489, AA809759, R20615, A1184905, H46838, AA029481, AA778585, R16041, AA253055, Z39839, H40110, AA483843, AA278627, R37936, H06060, R46123, AA282001, W04668, AA730323, H40174, AA215402, AA903630, AW304327, A1091241, AA885041, AA813856, and AC006263.</p>
HNGGR26	98	688054
HTLCX30	99	675636

HCEBC87	100	646713	AC002041, and AA132101.
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			AI253043, AA621792, N84222, AA094505, and AB020635.
			AI123531, W07173, AA480028, AI803282, AI708223, N62829, AI203954, AI094156, AA872061, N49953, AW005810, AA433846, AA411225, AA761754, AA745807, AI708531, N50810, AA243455, AA422108, AA824620, AI281390, R26124, AI246265, AA257995, AI766585, W01365, N78578, AA243448, AA761087, AA883328, AA257994, AA766741, AI361501, Z41792, AA479057, AA740668, AI868726, AA837149, Z46162, AA282715, N52735, N31703, N48176, and AB020653.
			AA359084, AC008149, AC006057, AC007308, AF064861, AL021329, AC005180, and AC005197.
HATCB92 HMSCX69	101 102	603948 692125	AI341807, AI651516, AI337376, W86648, N46466, AA522544, AI279721, W86523, AI245138, and AI262580.
			AL042250, R38741, F06975, R24942, T80007, R45205, Z40078, Z44674, F03694, AF070524, and D13896.
			AI620815, AL049064, AL042003, AA781401, AW248711, AI568876, R01265, AL044223, AA682242, AA887723, AW238884, AW372959, Y16610, AF090912, AF080514, AF080515, AF080512, AF080513, and AF080516.
			W27833, AI860764, AA809619, AA768248, AI370876, AI291737, H96013, AW051697, AI633038, and AI784315.
HLHAL68 HEOMR73 HETIB83 HJPDD28	103 104 105 106	684216 691244 690863 842041	
HBAMB15	107	671835	

[1285] Having generally described the invention, the same will be more readily understood by reference to the following examples, which are provided by way of illustration and are not intended as limiting.

### Examples

**[1286] Example 1: Isolation of a Selected cDNA Clone From the Deposited Sample**

[1287] Each cDNA clone in a cited ATCC deposit is contained in a plasmid vector. Table 1 identifies the vectors used to construct the cDNA library from which each clone was isolated. In many cases, the vector used to construct the library is a phage vector from which a plasmid has been excised. The table immediately below correlates the related plasmid for each phage vector used in constructing the cDNA library. For example, where a particular clone is identified in Table 1 as being isolated in the vector "Lambda Zap," the corresponding deposited clone is in "pBluescript."

<u>Vector Used to Construct Library</u>	<u>Corresponding Deposited</u>
<u>Plasmid</u>	
Lambda Zap	pBluescript (pBS)
Uni-Zap XR	pBluescript (pBS)
Zap Express	pBK
lafmid BA	plafmid BA
pSport1	pSport1
pCMVSPORT 2.0	pCMVSPORT 2.0
pCMVSPORT 3.0	pCMVSPORT 3.0
pCR <sup>®</sup> 2.1	pCR <sup>®</sup> 2.1

[1288] Vectors Lambda Zap (U.S. Patent Nos. 5,128,256 and 5,286,636), Uni-Zap XR (U.S. Patent Nos. 5,128, 256 and 5,286,636), Zap Express (U.S. Patent Nos. 5,128,256 and 5,286,636), pBluescript (pBS) (Short, J. M. et al., Nucleic Acids Res. 16:7583-7600 (1988); Altling-Mees, M. A. and Short, J. M., Nucleic Acids Res. 17:9494 (1989)) and pBK (Altling-Mees, M. A. et al., Strategies 5:58-61 (1992)) are



commercially available from Stratagene Cloning Systems, Inc., 11011 N. Torrey Pines Road, La Jolla, CA, 92037. pBS contains an ampicillin resistance gene and pBK contains a neomycin resistance gene. Both can be transformed into E. coli strain XL-1 Blue, also available from Stratagene. pBS comes in 4 forms SK+, SK-, KS+ and KS. The S and K refers to the orientation of the polylinker to the T7 and T3 primer sequences which flank the polylinker region ("S" is for SacI and "K" is for KpnI which are the first sites on each respective end of the linker). "+" or "-" refer to the orientation of the fl origin of replication ("ori"), such that in one orientation, single stranded rescue initiated from the fl ori generates sense strand DNA and in the other, antisense.

**[1289]** Vectors pSport1, pCMVSport 2.0 and pCMVSport 3.0, were obtained from Life Technologies, Inc., P. O. Box 6009, Gaithersburg, MD 20897. All Sport vectors contain an ampicillin resistance gene and may be transformed into E. coli strain DH10B, also available from Life Technologies. (See, for instance, Gruber, C. E., et al., Focus 15:59 (1993).) Vector lafmid BA (Bento Soares, Columbia University, NY) contains an ampicillin resistance gene and can be transformed into E. coli strain XL-1 Blue. Vector pCR<sup>®</sup>2.1, which is available from Invitrogen, 1600 Faraday Avenue, Carlsbad, CA 92008, contains an ampicillin resistance gene and may be transformed into E. coli strain DH10B, available from Life Technologies. (See, for instance, Clark, J. M., Nuc. Acids Res. 16:9677-9686 (1988) and Mead, D. et al., Bio/Technology 9: (1991).) Preferably, a polynucleotide of the present invention does not comprise the phage vector sequences identified for the particular clone in Table 1, as well as the corresponding plasmid vector sequences designated above.

**[1290]** The deposited material in the sample assigned the ATCC Deposit Number cited in Table 1 for any given cDNA clone also may contain one or more additional plasmids, each comprising a cDNA clone different from that given clone. Thus, deposits sharing the same ATCC Deposit Number contain at least a plasmid for each cDNA clone identified in Table 1. Typically, each ATCC deposit sample cited in Table 1 comprises a mixture of approximately equal amounts (by weight) of about 50 plasmid DNAs, each containing a different cDNA clone; but such a deposit sample

may include plasmids for more or less than 50 cDNA clones, up to about 500 cDNA clones.

**[1291]** Two approaches can be used to isolate a particular clone from the deposited sample of plasmid DNAs cited for that clone in Table 1. First, a plasmid is directly isolated by screening the clones using a polynucleotide probe corresponding to SEQ ID NO:X.

**[1292]** Particularly, a specific polynucleotide with 30-40 nucleotides is synthesized using an Applied Biosystems DNA synthesizer according to the sequence reported. The oligonucleotide is labeled, for instance, with  $^{32}\text{P}$ - $\gamma$ -ATP using T4 polynucleotide kinase and purified according to routine methods. (E.g., Maniatis et al., *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Press, Cold Spring, NY (1982).) The plasmid mixture is transformed into a suitable host, as indicated above (such as XL-1 Blue (Stratagene)) using techniques known to those of skill in the art, such as those provided by the vector supplier or in related publications or patents cited above. The transformants are plated on 1.5% agar plates (containing the appropriate selection agent, e.g., ampicillin) to a density of about 150 transformants (colonies) per plate. These plates are screened using Nylon membranes according to routine methods for bacterial colony screening (e.g., Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd Edit., (1989), Cold Spring Harbor Laboratory Press, pages 1.93 to 1.104), or other techniques known to those of skill in the art.

**[1293]** Alternatively, two primers of 17-20 nucleotides derived from both ends of the SEQ ID NO:X (i.e., within the region of SEQ ID NO:X bounded by the 5' NT and the 3' NT of the clone defined in Table 1) are synthesized and used to amplify the desired cDNA using the deposited cDNA plasmid as a template. The polymerase chain reaction is carried out under routine conditions, for instance, in 25  $\mu\text{l}$  of reaction mixture with 0.5  $\mu\text{g}$  of the above cDNA template. A convenient reaction mixture is 1.5-5 mM  $\text{MgCl}_2$ , 0.01% (w/v) gelatin, 20  $\mu\text{M}$  each of dATP, dCTP, dGTP, dTTP, 25 pmol of each primer and 0.25 Unit of Taq polymerase. Thirty five cycles of PCR (denaturation at 94 degree C for 1 min; annealing at 55 degree C for 1 min; elongation at 72 degree C for 1 min) are performed with a Perkin-Elmer Cetus automated thermal cycler. The amplified product is analyzed by agarose gel electrophoresis and

the DNA band with expected molecular weight is excised and purified. The PCR product is verified to be the selected sequence by subcloning and sequencing the DNA product.

**[1294]** Several methods are available for the identification of the 5' or 3' non-coding portions of a gene which may not be present in the deposited clone. These methods include but are not limited to, filter probing, clone enrichment using specific probes, and protocols similar or identical to 5' and 3' "RACE" protocols which are well known in the art. For instance, a method similar to 5' RACE is available for generating the missing 5' end of a desired full-length transcript. (Fromont-Racine et al., *Nucleic Acids Res.* 21(7):1683-1684 (1993).)

**[1295]** Briefly, a specific RNA oligonucleotide is ligated to the 5' ends of a population of RNA presumably containing full-length gene RNA transcripts. A primer set containing a primer specific to the ligated RNA oligonucleotide and a primer specific to a known sequence of the gene of interest is used to PCR amplify the 5' portion of the desired full-length gene. This amplified product may then be sequenced and used to generate the full length gene.

**[1296]** This above method starts with total RNA isolated from the desired source, although poly-A<sup>+</sup> RNA can be used. The RNA preparation can then be treated with phosphatase if necessary to eliminate 5' phosphate groups on degraded or damaged RNA which may interfere with the later RNA ligase step. The phosphatase should then be inactivated and the RNA treated with tobacco acid pyrophosphatase in order to remove the cap structure present at the 5' ends of messenger RNAs. This reaction leaves a 5' phosphate group at the 5' end of the cap cleaved RNA which can then be ligated to an RNA oligonucleotide using T4 RNA ligase.

**[1297]** This modified RNA preparation is used as a template for first strand cDNA synthesis using a gene specific oligonucleotide. The first strand synthesis reaction is used as a template for PCR amplification of the desired 5' end using a primer specific to the ligated RNA oligonucleotide and a primer specific to the known sequence of the gene of interest. The resultant product is then sequenced and analyzed to confirm that the 5' end sequence belongs to the desired gene.

**[1298] Example 2: Isolation of Genomic Clones Corresponding to a Polynucleotide**

[1299] A human genomic P1 library (Genomic Systems, Inc.) is screened by PCR using primers selected for the cDNA sequence corresponding to SEQ ID NO:X., according to the method described in Example 1. (See also, Sambrook.)

**[1300] Example 3: Tissue Distribution of Polypeptide**

[1301] Tissue distribution of mRNA expression of polynucleotides of the present invention is determined using protocols for Northern blot analysis, described by, among others, Sambrook et al. For example, a cDNA probe produced by the method described in Example 1 is labeled with P<sup>32</sup> using the rediprime™ DNA labeling system (Amersham Life Science), according to manufacturer's instructions. After labeling, the probe is purified using CHROMA SPIN-100™ column (Clontech Laboratories, Inc.), according to manufacturer's protocol number PT1200-1. The purified labeled probe is then used to examine various human tissues for mRNA expression.

[1302] Multiple Tissue Northern (MTN) blots containing various human tissues (H) or human immune system tissues (IM) (Clontech) are examined with the labeled probe using ExpressHyb™ hybridization solution (Clontech) according to manufacturer's protocol number PT1190-1. Following hybridization and washing, the blots are mounted and exposed to film at -70 degree C overnight, and the films developed according to standard procedures.

**[1303] Example 4: Chromosomal Mapping of the Polynucleotides**

[1304] An oligonucleotide primer set is designed according to the sequence at the 5' end of SEQ ID NO:X. This primer preferably spans about 100 nucleotides. This primer set is then used in a polymerase chain reaction under the following set of conditions : 30 seconds, 95 degree C; 1 minute, 56 degree C; 1 minute, 70 degree C. This cycle is repeated 32 times followed by one 5 minute cycle at 70 degree C. Human, mouse, and hamster DNA is used as template in addition to a somatic cell hybrid panel containing individual chromosomes or chromosome fragments (Bios,

Inc). The reactions is analyzed on either 8% polyacrylamide gels or 3.5 % agarose gels. Chromosome mapping is determined by the presence of an approximately 100 bp PCR fragment in the particular somatic cell hybrid.

**[1305] Example 5: Bacterial Expression of a Polypeptide**

**[1306]** A polynucleotide encoding a polypeptide of the present invention is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' ends of the DNA sequence, as outlined in Example 1, to synthesize insertion fragments. The primers used to amplify the cDNA insert should preferably contain restriction sites, such as BamHI and XbaI, at the 5' end of the primers in order to clone the amplified product into the expression vector. For example, BamHI and XbaI correspond to the restriction enzyme sites on the bacterial expression vector pQE-9. (Qiagen, Inc., Chatsworth, CA). This plasmid vector encodes antibiotic resistance (Amp<sup>r</sup>), a bacterial origin of replication (ori), an IPTG-regulatable promoter/operator (P/O), a ribosome binding site (RBS), a 6-histidine tag (6-His), and restriction enzyme cloning sites.

**[1307]** The pQE-9 vector is digested with BamHI and XbaI and the amplified fragment is ligated into the pQE-9 vector maintaining the reading frame initiated at the bacterial RBS. The ligation mixture is then used to transform the E. coli strain M15/rep4 (Qiagen, Inc.) which contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan<sup>r</sup>). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis.

**[1308]** Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.<sup>600</sup>) of between 0.4 and 0.6. IPTG (Isopropyl-B-D-thiogalacto pyranoside) is then added to a final concentration of 1 mM. IPTG induces by inactivating the lacI repressor, clearing the P/O leading to increased gene expression.

[1309] Cells are grown for an extra 3 to 4 hours. Cells are then harvested by centrifugation (20 mins at 6000Xg). The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl by stirring for 3-4 hours at 4 degree C. The cell debris is removed by centrifugation, and the supernatant containing the polypeptide is loaded onto a nickel-nitrilo-tri-acetic acid ("Ni-NTA") affinity resin column (available from QIAGEN, Inc., *supra*). Proteins with a 6 x His tag bind to the Ni-NTA resin with high affinity and can be purified in a simple one-step procedure (for details see: The QIAexpressionist (1995) QIAGEN, Inc., *supra*).

[1310] Briefly, the supernatant is loaded onto the column in 6 M guanidine-HCl, pH 8, the column is first washed with 10 volumes of 6 M guanidine-HCl, pH 8, then washed with 10 volumes of 6 M guanidine-HCl pH 6, and finally the polypeptide is eluted with 6 M guanidine-HCl, pH 5.

[1311] The purified protein is then renatured by dialyzing it against phosphate-buffered saline (PBS) or 50 mM Na-acetate, pH 6 buffer plus 200 mM NaCl. Alternatively, the protein can be successfully refolded while immobilized on the Ni-NTA column. The recommended conditions are as follows: renature using a linear 6M-1M urea gradient in 500 mM NaCl, 20% glycerol, 20 mM Tris/HCl pH 7.4, containing protease inhibitors. The renaturation should be performed over a period of 1.5 hours or more. After renaturation the proteins are eluted by the addition of 250 mM imidazole. Imidazole is removed by a final dialyzing step against PBS or 50 mM sodium acetate pH 6 buffer plus 200 mM NaCl. The purified protein is stored at 4 degree C or frozen at -80 degree C.

[1312] In addition to the above expression vector, the present invention further includes an expression vector comprising phage operator and promoter elements operatively linked to a polynucleotide of the present invention, called pHE4a. (ATCC Accession Number 209645, deposited on February 25, 1998.) This vector contains: 1) a neomycinphosphotransferase gene as a selection marker, 2) an E. coli origin of replication, 3) a T5 phage promoter sequence, 4) two lac operator sequences, 5) a Shine-Delgarno sequence, and 6) the lactose operon repressor gene (lacIq). The origin of replication (oriC) is derived from pUC19 (LTI, Gaithersburg, MD). The promoter sequence and operator sequences are made synthetically.

[1313] DNA can be inserted into the pHEa by restricting the vector with NdeI and XbaI, BamHI, XhoI, or Asp718, running the restricted product on a gel, and isolating the larger fragment (the stuffer fragment should be about 310 base pairs). The DNA insert is generated according to the PCR protocol described in Example 1, using PCR primers having restriction sites for NdeI (5' primer) and XbaI, BamHI, XhoI, or Asp718 (3' primer). The PCR insert is gel purified and restricted with compatible enzymes. The insert and vector are ligated according to standard protocols.

[1314] The engineered vector could easily be substituted in the above protocol to express protein in a bacterial system.

**[1315] Example 6: Purification of a Polypeptide from an Inclusion Body**

[1316] The following alternative method can be used to purify a polypeptide expressed in *E. coli* when it is present in the form of inclusion bodies. Unless otherwise specified, all of the following steps are conducted at 4-10 degree C.

[1317] Upon completion of the production phase of the *E. coli* fermentation, the cell culture is cooled to 4-10 degree C and the cells harvested by continuous centrifugation at 15,000 rpm (Heraeus Sepatech). On the basis of the expected yield of protein per unit weight of cell paste and the amount of purified protein required, an appropriate amount of cell paste, by weight, is suspended in a buffer solution containing 100 mM Tris, 50 mM EDTA, pH 7.4. The cells are dispersed to a homogeneous suspension using a high shear mixer.

[1318] The cells are then lysed by passing the solution through a microfluidizer (Microfluidics, Corp. or APV Gaulin, Inc.) twice at 4000-6000 psi. The homogenate is then mixed with NaCl solution to a final concentration of 0.5 M NaCl, followed by centrifugation at 7000 xg for 15 min. The resultant pellet is washed again using 0.5M NaCl, 100 mM Tris, 50 mM EDTA, pH 7.4.

[1319] The resulting washed inclusion bodies are solubilized with 1.5 M guanidine hydrochloride (GuHCl) for 2-4 hours. After 7000 xg centrifugation for 15 min., the pellet is discarded and the polypeptide containing supernatant is incubated at 4 degree C overnight to allow further GuHCl extraction.

[1320] Following high speed centrifugation (30,000 xg) to remove insoluble particles, the GuHCl solubilized protein is refolded by quickly mixing the GuHCl extract with 20 volumes of buffer containing 50 mM sodium, pH 4.5, 150 mM NaCl, 2 mM EDTA by vigorous stirring. The refolded diluted protein solution is kept at 4 degree C without mixing for 12 hours prior to further purification steps.

[1321] To clarify the refolded polypeptide solution, a previously prepared tangential filtration unit equipped with 0.16 um membrane filter with appropriate surface area (e.g., Filtron), equilibrated with 40 mM sodium acetate, pH 6.0 is employed. The filtered sample is loaded onto a cation exchange resin (e.g., Poros HS-50, Perseptive Biosystems). The column is washed with 40 mM sodium acetate, pH 6.0 and eluted with 250 mM, 500 mM, 1000 mM, and 1500 mM NaCl in the same buffer, in a stepwise manner. The absorbance at 280 nm of the effluent is continuously monitored. Fractions are collected and further analyzed by SDS-PAGE.

[1322] Fractions containing the polypeptide are then pooled and mixed with 4 volumes of water. The diluted sample is then loaded onto a previously prepared set of tandem columns of strong anion (Poros HQ-50, Perseptive Biosystems) and weak anion (Poros CM-20, Perseptive Biosystems) exchange resins. The columns are equilibrated with 40 mM sodium acetate, pH 6.0. Both columns are washed with 40 mM sodium acetate, pH 6.0, 200 mM NaCl. The CM-20 column is then eluted using a 10 column volume linear gradient ranging from 0.2 M NaCl, 50 mM sodium acetate, pH 6.0 to 1.0 M NaCl, 50 mM sodium acetate, pH 6.5. Fractions are collected under constant  $A_{280}$  monitoring of the effluent. Fractions containing the polypeptide (determined, for instance, by 16% SDS-PAGE) are then pooled.

[1323] The resultant polypeptide should exhibit greater than 95% purity after the above refolding and purification steps. No major contaminant bands should be observed from Commassie blue stained 16% SDS-PAGE gel when 5 ug of purified protein is loaded. The purified protein can also be tested for endotoxin/LPS contamination, and typically the LPS content is less than 0.1 ng/ml according to LAL assays.



**[1324] Example 7: Cloning and Expression of a Polypeptide in a Baculovirus Expression System**

[1325] In this example, the plasmid shuttle vector pA2 is used to insert a polynucleotide into a baculovirus to express a polypeptide. This expression vector contains the strong polyhedrin promoter of the *Autographa californica* nuclear polyhedrosis virus (AcMNPV) followed by convenient restriction sites such as BamHI, Xba I and Asp718. The polyadenylation site of the simian virus 40 ("SV40") is used for efficient polyadenylation. For easy selection of recombinant virus, the plasmid contains the beta-galactosidase gene from *E. coli* under control of a weak *Drosophila* promoter in the same orientation, followed by the polyadenylation signal of the polyhedrin gene. The inserted genes are flanked on both sides by viral sequences for cell-mediated homologous recombination with wild-type viral DNA to generate a viable virus that express the cloned polynucleotide.

[1326] Many other baculovirus vectors can be used in place of the vector above, such as pAc373, pVL941, and pAcIM1, as one skilled in the art would readily appreciate, as long as the construct provides appropriately located signals for transcription, translation, secretion and the like, including a signal peptide and an in-frame AUG as required. Such vectors are described, for instance, in Luckow et al., *Virology* 170:31-39 (1989).

[1327] Specifically, the cDNA sequence contained in the deposited clone, including the AUG initiation codon and the naturally associated leader sequence identified in Table 1, is amplified using the PCR protocol described in Example 1. If the naturally occurring signal sequence is used to produce the secreted protein, the pA2 vector does not need a second signal peptide. Alternatively, the vector can be modified (pA2 GP) to include a baculovirus leader sequence, using the standard methods described in Summers et al., "A Manual of Methods for Baculovirus Vectors and Insect Cell Culture Procedures," Texas Agricultural Experimental Station Bulletin No. 1555 (1987).

[1328] The amplified fragment is isolated from a 1% agarose gel using a commercially available kit ("GeneClean," BIO 101 Inc., La Jolla, Ca.). The fragment

then is digested with appropriate restriction enzymes and again purified on a 1% agarose gel.

[1329] The plasmid is digested with the corresponding restriction enzymes and optionally, can be dephosphorylated using calf intestinal phosphatase, using routine procedures known in the art. The DNA is then isolated from a 1% agarose gel using a commercially available kit ("Geneclean" BIO 101 Inc., La Jolla, Ca.).

[1330] The fragment and the dephosphorylated plasmid are ligated together with T4 DNA ligase. *E. coli* HB101 or other suitable *E. coli* hosts such as XL-1 Blue (Stratagene Cloning Systems, La Jolla, CA) cells are transformed with the ligation mixture and spread on culture plates. Bacteria containing the plasmid are identified by digesting DNA from individual colonies and analyzing the digestion product by gel electrophoresis. The sequence of the cloned fragment is confirmed by DNA sequencing.

[1331] Five ug of a plasmid containing the polynucleotide is co-transfected with 1.0 ug of a commercially available linearized baculovirus DNA ("BaculoGold™ baculovirus DNA", Pharmingen, San Diego, CA), using the lipofection method described by Felgner et al., Proc. Natl. Acad. Sci. USA 84:7413-7417 (1987). One ug of BaculoGold™ virus DNA and 5 ug of the plasmid are mixed in a sterile well of a microtiter plate containing 50 ul of serum-free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards, 10 ul Lipofectin plus 90 ul Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to Sf9 insect cells (ATCC CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is then incubated for 5 hours at 27 degrees C. The transfection solution is then removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. Cultivation is then continued at 27 degrees C for four days.

[1332] After four days the supernatant is collected and a plaque assay is performed, as described by Summers and Smith, *supra*. An agarose gel with "Blue Gal" (Life Technologies Inc., Gaithersburg) is used to allow easy identification and isolation of gal-expressing clones, which produce blue-stained plaques. (A detailed description of a "plaque assay" of this type can also be found in the user's guide for insect cell